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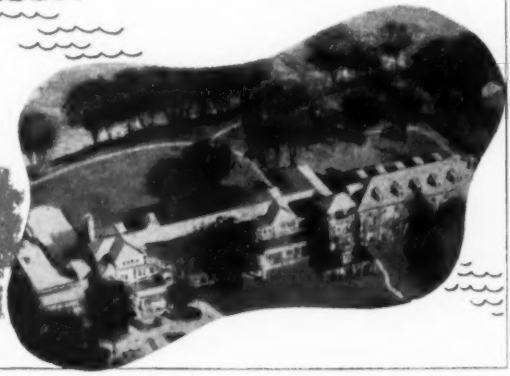

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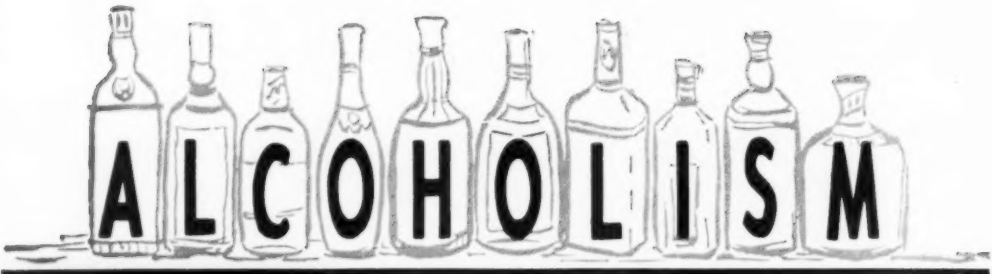

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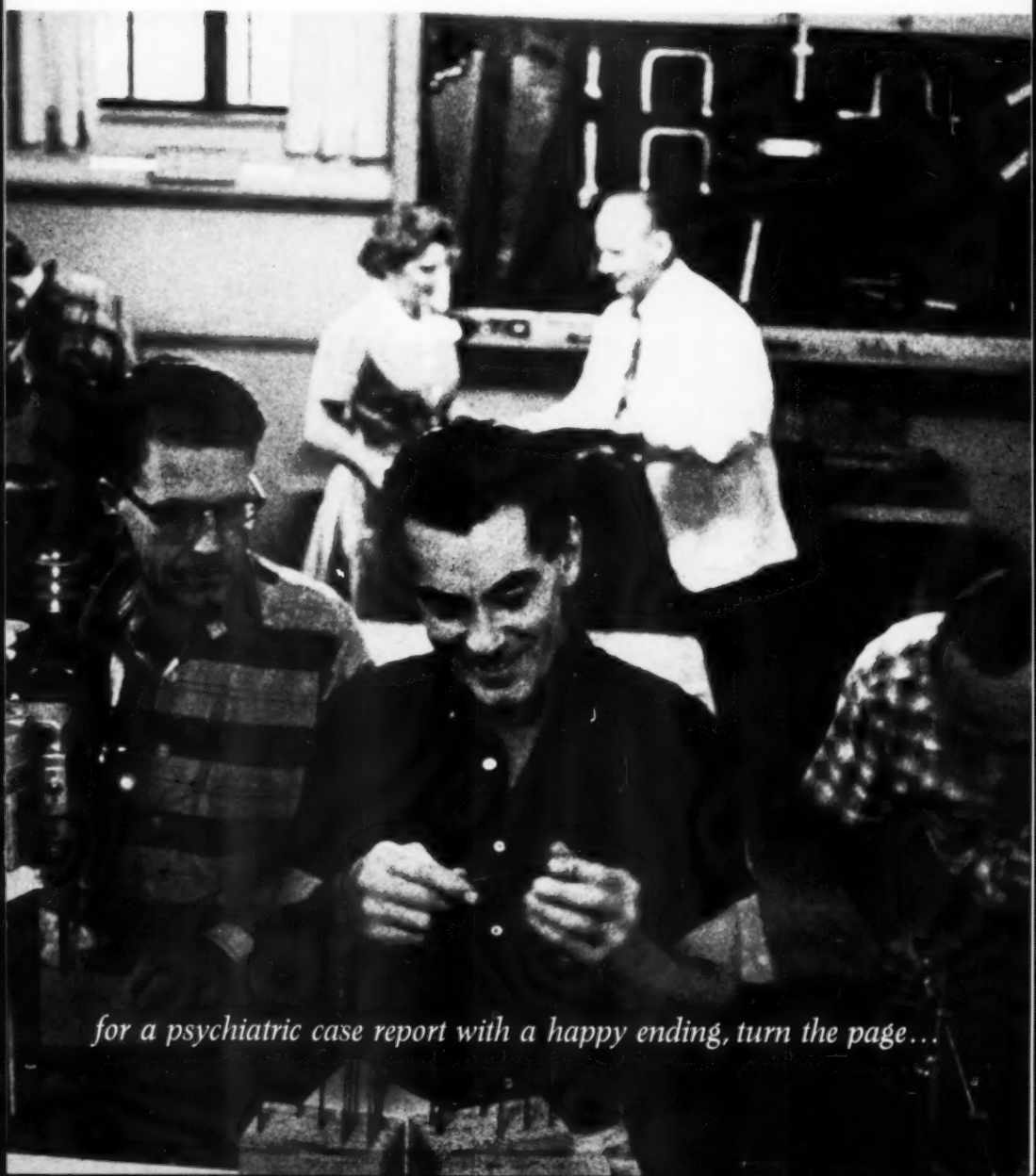

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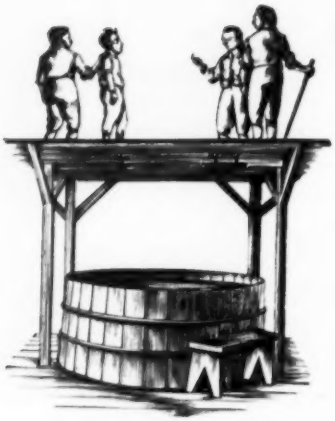

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1. Graffagnino, P. N., Friel, P. B. and Zeller, W. W.: Emotional disorders treated with meprobamate and promazine. Connecticut M. J. 21:1047, Dec. 1957.

SYMPTOMATIC IMPROVEMENT

(hospitalized patients—all types)

by disease

DIAGNOSIS	NO. OF PATIENTS	NO. IMPROVED
SCHIZOPHRENIA		
PARANOID	7	2
NON-PARANOID	45	34
DEPRESSION		
PSYCHOTIC†	37	25
NEUROTIC	16	10
ANXIETY STATE	9	8
CHARACTER DISORDERS	15	13
OTHERS	16	13
TOTALS	145	105

by symptom

SYMPTOM	NO. IMPROVED
SLEEP DISTURBANCES	36
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SECTION ON
NEUROLOGY

Central Neurogenic Hyperventilation in Man

FRED PLUM, M.D., and AUGUST G. SWANSON, M.D., Seattle

Centrally caused respiratory facilitation was first suggested to us by the unusually heavy breathing of several patients recovering from the effects of transient exposures to acute anoxia. There was no carboxyhemoglobin, persisting anoxemia, cardiac disease, or pulmonary abnormality to stimulate a compensatory hyperpnea; yet several overbreathed themselves into clinical tetany while still in deep coma. Subsequently, the same respiratory pattern was observed in patients with hypoglycemia, severe head injuries, and acute cerebral vascular lesions. Several of these patients were in younger age groups and were completely free of cardiopulmonary disease. Autopsies showed severe brain stem changes, but either the lesions were too diffuse to afford specific conclusions on the neuroanatomy involved or the respiratory changes had not been quantitated adequately. Descriptions of "forced," "heavy," or "stertorous" breathing in the case reports of patients with fulminating meningitis,[1,2] basilar artery thrombosis,[3,4] pontile hemorrhage,[5] and encephalitis[6] supported the impression that forced breathing is a manifestation of brain stem dysfunction. However, neither quantitative studies of the hyperpnea nor any specific explanation for its cause could be found.

The present study demonstrates that the forced breathing which accompanies certain kinds of brain lesions produces an intense hyperventilation. Furthermore, the hyperventilation appears to be directly neurogenic, resulting from damage to specific regions in the central brain stem.

Material and Method

The clinical and physiological findings in nine patients who developed severe hyperventilation during the course of acute central nervous system disease are detailed. Contrasting data are presented on 25 other patients who had acute brain lesions but who lacked clinical hyperventilation. A brief summary of the pathological neuroanatomy found in six of the subjects with hyperventilation is included for completeness.

Patients were selected from the neurological unit and medical wards of the King County Hospital. Meticulous clinical examinations were supplemented by appropriate clinical laboratory studies. The cardiovascular system was evaluated in detail, and, when indicated, the serum electrolytes were determined in order to assess extraneural factors influencing the respiration. Ten subjects, six with hyperventilation and four controls, had complete autopsies.

The respiratory pattern was measured with a strain-gauge pneumograph. The carbon dioxide tension of the *expired* air was continuously analyzed with a Liston-Becker infrared CO_2 analyzer; the alveolar carbon dioxide ($PACO_2$) was taken as the value recorded at the end of expiration (end-tidal volume). Arterial blood samples were analyzed in duplicate. The arterial pH was determined on freshly drawn blood at 37 C with a Coleman microchamber electrode attached to a Cambridge Model R pH meter. The arterial oxygen and carbon dioxide contents were determined by the Van

Received for publication May 22, 1958.

From the Department of Medicine, Division of Neurology, University of Washington School of Medicine.

These studies were aided by grants from Initiative 171 Fund of the State of Washington, the U. S. Public Health Service, and an annual grant from the National Foundation for Infantile Paralysis to the Northwest Respirator and Rehabilitation Center.

Slyke manometric technique, and the arterial carbon dioxide tension ($PaCO_2$) was calculated from the Singer-Hastings nomogram.[7] The minute ventilation was measured through a respiratory valve attached to a tight-fitting face mask and connected to either a Tissot or a Benedict-Roth spirometer. Respiratory dead space for the males was estimated at either 150 or 170 cc. The combined dead space of face mask and respiratory valve was 70 cc. Alveolar ventilation was estimated by subtracting dead-space ventilation from minute ventilation. The respiratory response to CO_2 was determined by one of two methods: 1. The subject rebreathed his own CO_2 from the spirometer, during which time $PACO_2$ and breath-to-breath ventilation were measured, or, 2. the subject inhaled known concentrations of CO_2 from a Tissot chamber for a period lasting from 5 to 10 minutes, during which time the $PACO_2$ was continuously monitored. The periods of CO_2 inhalation were not carried to the usual 20-30 minutes, because it was not desirable to prolong the intense hyperpnea in such severely ill patients. Constant ventilation of at least three minutes' duration was obtained in determining the response to CO_2, and the minute ventilation, corrected to BTPS (body temperature and pressure, saturated with water), was calculated as the mean of the last three minutes.

Brains removed from patients at autopsy were fixed in 10% formalin and sectioned coronally through the hemispheres at intervals of 1 cm. and through the brain stem at intervals of 3-4 mm. Appropriate blocks from the hemispheres and all blocks from the brain stem were embedded in paraffin. Sections from each block were stained by the Weigert, Nissl, and hematoxylin-eosin methods. Details of the anatomical studies will be presented elsewhere.

Observations

I. Hyperventilation Associated with Pontile Lesions

Clinical Observations.—The clinical appearance of the respiration which excited interest in these patients consisted of a metronomically regular, moderately deep, rapid, and labored breathing pattern, which lasted for hours or days at a time (Fig. 1). Inspiratory and expiratory phases of the respiratory cycle were equal in length, expiration usually being active rather than passive. Clinical inspection of the respiratory abnormality suggested a profound hyperventilation, the hyperpnea resembling the breathing pattern seen in patients with severe metabolic acidosis or in subjects performing intense muscular exercise. Since the respiratory abnormality appeared to be an integral part of the neurological illness, it was called central hyperventilation.

The brief protocols in the "Appendix" list the salient clinical, laboratory, and pathological findings in the nine patients showing central hyperventilation. Abnormalities present in any system which could have influenced the respiration are included in the summaries. Each patient had clinical evidence of severe dysfunction at the pontile-midbrain level. Stupor or coma was present in every subject at the time when the respiratory defect developed. Seven had

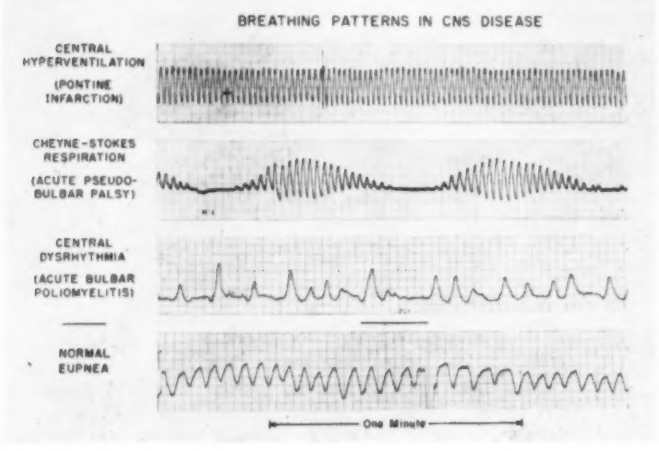


Fig. 1.—These are qualitative pneumographic recordings run at identical paper speeds. Inspiration in this and in subsequent records reads up. Note the metronomic regularity of central hyperventilation, as compared with the other respiratory patterns.

become unconscious suddenly or had been found in unexplained coma by their families, while two declined gradually into coma during the first 48 hours of hospitalization. All nine were desperately ill, and only one patient, a woman with illuminating (coal) gas poisoning, survived.

Abnormalities in the pupils and extraocular movements reflected the centrally placed brain stem lesions. The pupils usually were fixed, were often unequal, and tended to be markedly constricted. The external eye movements showed skew deviations or dysconjugate motion. An anterior internuclear ophthalmoplegia was demonstrated by caloric tests in four subjects.[8]

Except for a third nerve paralysis and a unilateral peripheral facial nerve paralysis in two patients, peripheral cranial nerve defects were absent. Every patient had bilateral extensor plantar responses, and eight showed periods of bilateral decerebrate rigidity. Only one patient maintained bilaterally flaccid extremities throughout his hospitalization, but the neurological signs in the others fluctuated considerably and intermittent flaccidity was frequent. Seven subjects showed diffuse flaccidity at some time during hospitalization. Testing of sensation was impossible.

Close attention was paid to the duration of hyperventilation and its relationship to other physical and neurological signs. In no patient did the hyperventilation last throughout the entire hospital stay, although the respiratory defect, when fully developed, lasted from hours to days at a time. The onset of the hyperpnea coincided with the acute onset of other signs of brain stem disease in three patients, whereas in the others hyperventilation developed at varying points during their illness. Only three subjects experienced hyperventilation for the first time within 24 hours before death. The development of hyperventilation could not be correlated with the development of abnormal findings in the lungs, heart, or circulation. Elimination of respiratory obstruction by means of oral airways, careful patient positioning, and tracheotomy (two patients) failed to alter the overbreathing.

Except for coma and bilateral extensor plantar responses, there was no single neurological abnormality that invariably accompanied central hyperventilation. Trismus, diffuse neuromuscular excitability, and abnormal posturing of the hands reflected the associated development of tetany in at least three patients. Since hyperventilation in some patients developed in the absence of decerebrate rigidity, the neural mechanisms facilitating the breathing were not identical with those which facilitate peripheral skeletal-muscle stretch reflexes. When hyperventilation coincided with periods of decerebrate rigidity, however, it was more intense than the hyperpnea which coincided with periods of diffuse flaccidity. Furthermore, whenever the decerebrate rigidity increased in degree, respiration was simultaneously augmented. This increase occurred particularly during expiration.

Other respiratory abnormalities were frequent in these patients. Two had singultus, and six had periodic respirations of the Cheyne-Stokes type at some time during their illness. Periodic breathing, when it occurred, usually preceded central hyperventilation, and the latter usually was associated with progression of the neurological illness. The quality of the Cheyne-Stokes respiration observed in patients with pontile lesions did not differ from periodic breathing accompanying lesions in other parts of the brain. The cycles of hyperpnea and hypopnea appeared with a rhythmically spaced frequency and showed great symmetry between the crescendo and the decrescendo phase of each cycle (Fig. 1). The periodicity could be reduced or eliminated either by oxygen therapy or by carbon dioxide inhalations (Fig. 5). Direct blood studies during the Cheyne-Stokes breathing were performed on two subjects who at other times showed hyperventilation. Both showed findings similar to those listed in Table 3 for the patients with periodic breathing, namely, a moderately decreased or low-normal

arterial oxygen saturation combined with a lowered $PaCO_2$.

Lumbar punctures were performed on all nine patients. Increased intracranial pressure was present only in the two subjects with cerebral hemorrhages. Fluids in the remainder were crystal-clear, the only abnormality being a moderate increase in protein content in several.

As might be expected, disturbances in body systems outside the brain were frequent. The clinical protocols summarize the abnormalities detected on the general medical examinations. The descriptions of x-rays and the clinical examination of the lungs are given in respect to the time that ventilation studies were performed.

Quantitative Respiratory Studies.—Tables 1 and 2 summarize the blood gas findings and respiratory changes in these nine patients. Direct measurements confirmed the clinical impression of severe hyperventilation. The respiratory rates were rapid (28-38 per minute); the tidal volumes were comparatively deep, and the minute ventilations and estimated minute alveolar ventilations at rest ranged from one and one-half to more than four times the normal level. Arterial blood analyses demonstrated marked hypocapnia, with a mean $PaCO_2$ of 24.2 mm. Hg, and alkalosis, with a mean pH of 7.48.

TABLE 1.—*Alveolar and Arterial Blood Gas Values in Central Hyperventilation*

		Arterial			
Case	$PACO_2$ Mm. Hg	O_2 % Sat.	pH	CO_2 mM/L.	$PaCO_2$ Mm. Hg
Normal adults, this lab	38±2	95±2	7.42±0.02	22±2	40±2
1		95.0	7.52	14.0	19
2	19	94.1	7.52	13.5	19
3	21	94.4	7.51	13.8	22
4	20	97.5	7.42	12.6	24
5	20				24 *
6	20	96.5	7.41	11.4	24
7		93.1	7.49	18.2	30
8	24	92.1	7.49		28 *
9		93.0	7.44	15.8	28
Mean		94.5±1.9	7.48±0.048	14.2±2.22	24.2±3.9

* Estimated from $PACO_2$; direct arterial CO_2 content not estimated.

The hyperventilation could not be attributed to anoxemia, since the arterial oxygen saturations were essentially normal (mean 94.5 vol. %). As an additional check against anoxemia, 100% oxygen was given by mask to five patients: The breathing patterns, $PACO_2$ values, and ventilation volumes showed no significant changes in any.

The central neural structures regulating respiration retained their sensitivity to additional reflex and chemical stimulation despite the considerable hyperpnea present at rest (Table 2). Painful supraorbital pressure or vigorous pinching of tendons increased the minute volume and further lowered the $PACO_2$. This effect was achieved primarily by increasing respiratory rate.

The effect on ventilation of increased concentrations of carbon dioxide in the inspired air was measured in three subjects. Each showed a marked increase in minute volume, primarily by increasing the depth rather than the rate of respiration. When the ventilation during CO_2 inhalation was expressed as a multiple of the resting ventilation on air, the per cent of increase in breathing per millimeter Hg, rise in $PACO_2$, was less than in normals.[9,10] This may have been the result of the high resting minute ventilation, since the absolute increase in ventilation per millimeter Hg, rise in $PACO_2$, averaged 1.32 liter, which approached closely the response which is obtained when CO_2 sensitivity is determined in normals at rest.[10] Figure 2 illustrates graphically these respiratory responses in Case 2.

Pathological Studies.—Autopsies were performed on six subjects who had central hyperventilation. By the time death occurred, each had suffered moderate to extensive bronchopneumonia or pulmonary congestion. These complications were not different from the pulmonary findings encountered almost routinely at this hospital among nonhyperpneic patients dying in coma from other causes. Three patients had serious heart lesions. The case protocols in the Appendix summarize the principal sys-

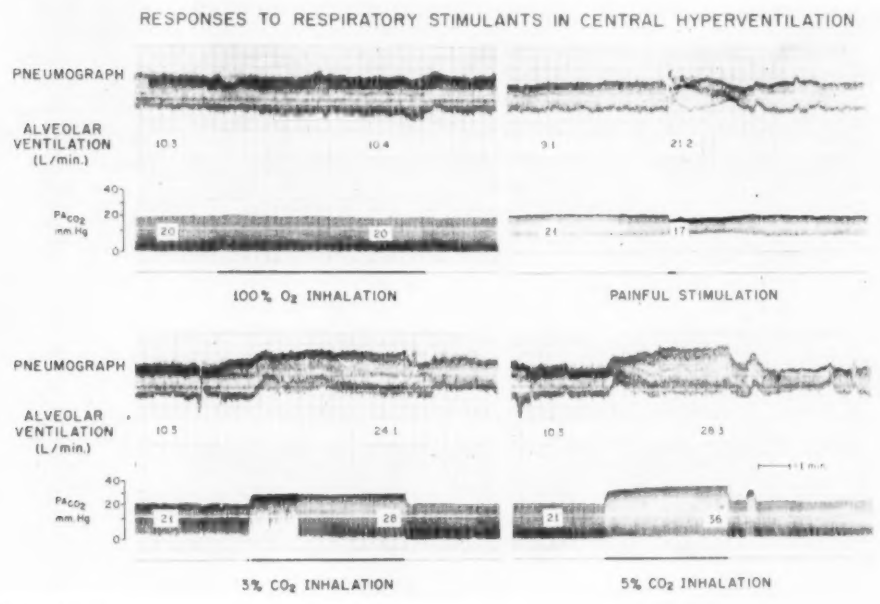
TABLE 2.—*Respiratory Studies in Central Hyperventilation*

Case	Normal *	2	4	5	6	9
Resting						
f (respiratory frequency/min.)	12–16	36	28	38	30	22
V_E (L/min., ventilation)	5.1–6.4	18.3		24.6	24.8	10.9
V_A (L/min., alveolar ventilation)	3.4–4.2	10.3		15.5	17.4	7.5
$PACO_2$, mm. Hg	37–39	21		20	16	28
Response to 3% CO_2						
f		38			31	
V_E		32.3			36.1	
V_A		24.1			28.6	
$PACO_2$		28			27	
L/min/mm. Hg †	2.02	1.97			1.02	
Response to 5% CO_2						
f		38		38	31	
V_E		36.5		43.8	50.8	
V_A		28.3		37.6	43.3	
$PACO_2$		36		43	34	
L/min/mm. Hg	2.02	1.20		.96	1.44	
Response to pain						
f		44	38	40	36	
V_E		30.9				
V_A		21.2				
$PACO_2$		17	17.7	17	16	
Response to 100% oxygen						
f		36	no	38	38	22
V_E		18.9	apparent	24.1	25.0	11.2
V_A		10.4	change	15.0	17.6	7.8
$PACO_2$		21		20	17	

* Based on estimated body surface area of 1.7 sq. m.

† Increase in liters of alveolar ventilation per minute per millimeter Hg increase in $PACO_2$.

Fig. 2.—Responses to respiratory stimuli in Case 2. The pneumographic diagrams are qualitative only. The measurements of ventilation recorded during these observations were obtained with a Tissot spirometer. Base-line marks indicate the duration of the stimulus in each observation.



temic abnormalities found in the general autopsies.

Examinations of the brains showed necrosis of the central portion of the pons in five cases and compression of the pons in the sixth. The necrosis in four brains was due to occlusion of the medial perforating branches of the basilar artery in association with a thrombosis or an embolus of the midpontile portion of the basilar artery. In two brains hemorrhages had originated above the tentorium and produced incisural herniation with midbrain compression and central midbrain-pontile hemorrhage. One of the four brains showing basilar artery thrombosis also contained an acute hemispheric infarction. In the remaining three specimens the lesions were confined to the brain stem.

The four brains presenting necrosis of the medial pons provided the most discrete changes for anatomic analysis. The full anatomic details of these four cases, along with additional cases in which hyperventilation was documented clinically, will be presented elsewhere. The medial basis pontis was partially necrotic, and the lesions extended to include large portions of the medial pontile tegmentum dorsally as far as the aqueduct. Laterally, the basis pontis showed necrosis, which was variable in extent. Dorsolaterally placed structures, including almost the entire lateral pontile tegmentum, were largely spared, usually on both sides. In no instance did the necrotic area extend caudally farther than a level 4-5 mm. above the pontomedullary junction. In one brain, where an embolus had lodged in the basilar artery, a 1 mm. area of central necrosis, interposed between the red nuclei, was the only damage found above the midbrain-pontile junction (Fig. 3). Thus, the lesions common to all these brains involved major parts of the corticospinal tracts in the pons, and the basal pontile nuclei, particularly medially, and variable amounts of the medial pontile reticular formation, the medial lemniscus, and the medial longitudinal fasciculus. The lateral pontile reticular formation, the vestibular nuclei,

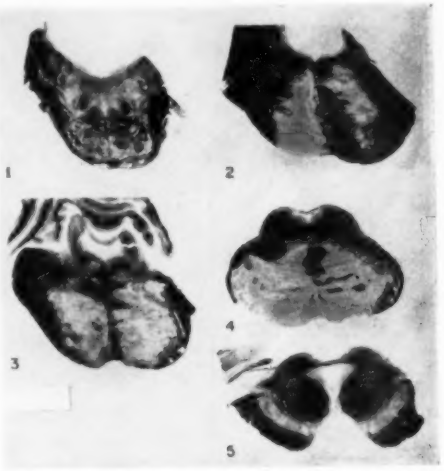


Fig. 3.—Myelin sections of the brain stem in Case 9. There were no lesions at the pontomedullary junction. The demyelinated areas in Sections *2*, *3*, and *4* are evident. In Section *5* there was a submacroscopic area of necrosis interposed between the red nuclei.

and laterally placed fiber tracts were largely or completely spared. The medulla oblongata and the caudal end of the entire pons were spared in every case.

II. Respiratory Changes with Nonpontile Lesions

Both the clinical and the pathological observations summarized in Section I indicated extensive damage to the medial pons in subjects who had the metronomic tachypnea that was called "central hyperventilation." Similar patterns of breathing were not clinically observed in any of a large group of patients in this hospital in whom autopsy showed brain lesions sparing the pontile region. Many of these latter subjects, however, had cardiopulmonary abnormalities that were as extensive as those which were found in subjects with central hyperventilation. Hence the abnormal breathing pattern of central hyperventilation appeared to be specific for patients with pontile disease.

As an additional check on the specificity of the respiratory abnormality in pontile disease, blood gas studies were performed on 25 patients with cerebral infarction involving various parts of the brain but spar-

ing the pons. Most of these control subjects were elderly, and many were seriously ill with brain lesions, producing marked neurological impairment. As was the case in selecting cases with central hyperventilation, patients with clinical anoxemia, frank congestive failure, or extensive pneumonitis were excluded. Even with the precautions, it was almost impossible to find persons with significant cerebral vascular disease who were completely free of manifestations of cardiopulmonary disease. The incidence of latent cardiopulmonary problems was at least as great in the controls as was encountered among the patients with pontile lesions.

Among the 25 control patients, the neurological lesions were localized by clinical examination in 21 and at autopsy in 4. The clinical differentiation of disease in the anterior from disease in the posterior cerebral circulation was difficult in some patients, particularly when bilateral neurological signs were present. Five patients had brain stem infarctions: Two showed akinetic mutism due to presumed diencephalic lesions, and three had lateral medullary syndromes. Seven patients had bilateral hemispheric lesions, and 11 patients had massive unilateral hemispheric lesions. Two of the patients with brain stem disease, five of those with bilateral hemispheric disease, and one subject with unilateral hemispheric disease had Cheyne-Stokes breathing at the time of study. Arterial bloods were drawn from the periodic breathers throughout the apneic and hyperpneic phases of a respiratory cycle.

Table 3 lists the results of arterial blood gas analyses for the control patients with regular breathing, and Table 4 gives these values for the control patients with periodic breathing. Several patients in both groups were moderately anoxemic. Despite this potential respiratory stimulus, the mean values for both carbon dioxide contents and $PaCO_2$ were significantly ($P<0.001$) higher among the controls than among the subjects

TABLE 3.—*Arterial Blood Gas Studies in Cerebral Infarction with No Apparent Respiratory Abnormalities*

Case	Age	Sex	Lesion	O_2, % Sat.	pH	CO_2, mM/L.	$PaCO_2$ Mm. Hg
Brain stem lesions							
A	57	M	Akinetic mute	93.3	7.41	19.2	37
B	72	M	CBLL hemorrhage	85.6	7.37	15.0	30
C	75	M	R. post. inf. CBLL a. thrombus	93.7	7.45	21	36
D	78	F	Akinetic mute	94.1	7.48	19.8	32
E	77	M	Akinetic mute	98.5	7.45	24.2	43
Mean				93.0±4.6	7.43±0.032	19.8±3.3	35.6±5.0
Bilateral hemispheric lesions							
F	68	M	Pseudobulbar palsy	89.8	7.40	22.8	43
G	76	M	Bilat. hemiparesis	90.5	7.43	18.4	33
H	86	M	R. frontal hemorr.; L. capsular infarct	87.8	7.41	21.2	38
Mean				89.4±1.4	7.41±0.013	20.8±1.7	38.0±5.0
Unilateral hemispheric lesions							
I	49	M	R. hemiplegia	91.1	7.44	20.0	37
J	67	M	R. hemiplegia	92.4	7.46	23.4	40
K	65	M	R. hemiplegia	92.7	7.40	19.5	39
L	70	F	L. hemiplegia	91.3	7.48	17.2	28
M	73	F	R. hemiplegia	91.2	7.44	17.8	31
N	74	M	L. hemisensory	92.7	7.41	20.2	37
O	75	F	L. hemiparesis	91.8	7.41	21.4	40
P	75	F	L. hemiplegia	92.5	7.48	19.3	31
Q	76	F	R. hemiplegia	94.2	7.49	20.8	33
Mean				92.2±1.0	7.44±0.033	19.9±1.85	35.1±5.0

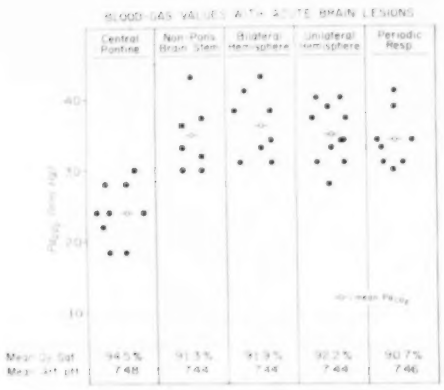


Fig. 4.—The individual $PaCO_2$ plots and the mean oxygen saturation and arterial pH values in the middle three groups include patients with both regular and periodic breathing. Thus, values on subjects with periodic breathing appear twice in this figure. The tables should be consulted for details.

with pontile lesions (Table 1). The mean arterial pH was lower in each control group than the mean pH found in central hyperventilation. No controls were found with the severe hypocapnia sometimes observed in central hyperventilation. Indeed, as Figure 4 illustrates, there was very little overlap in individual $PaCO_2$ values between the hyperventilation and the control groups.

Although significantly different from the values observed with central hyperventilation, the mean $PaCO_2$ of subjects with cerebral vascular disease was lower than is normally found in healthy young adults. The mean pH was elevated toward the alkalotic side, and the mean oxygen saturation was on the low side of normal. It is our impression that these changes reflected the frequent association of subclinical circulatory and pulmonary abnormalities with cerebral vascular disease. Several patients in each control group had quite normal arterial CO_2 tensions. It appeared unlikely that hyperventilation was neurogenic in others among the controls with apparently identical brain lesions.

More extensive studies on the complex problem of Cheyne-Stokes breathing in patients with neurological disease will be reported subsequently. Data are presented here only to indicate that when periodic breathing is corrected, central hyperventilation does not ensue. Table 4 indicates that subjects with periodic breathing frequently were anoxemic. Figure 5 illustrates the phasic changes which take place in Cheyne-Stokes respiration and the alterations produced in the blood gases when periodic breathing is ameliorated by either O_2 or CO_2 inhalations. During periodic breathing a relative anoxemia and a normal carbon dioxide tension combine to initiate hyperpnea, which rapidly produces a normal oxygen saturation and hypocapnia. At this point apnea develops, during which the $PaCO_2$ rises and anoxemia recurs. Preventing anoxemia by oxygen administration and preventing hyperventilation apnea by CO_2 administration both eliminate periodicity in respiration.[11] Also, during oxygen administration the arterial carbon dioxide tension remains above the levels usually associated with hyperventilation apnea,[12] while during CO_2 administration the arterial oxygen saturation often is maintained above the anoxemic range. Either gas given

TABLE 4.—*Arterial Blood Gas Studies in Cerebral Infarction with Periodic Breathing*

Case	Age	Sex	Lesion	O_2, % Sat.	pH	CO_2, mM/L.	$PaCO_2$ Mm. Hg
R	63	M	Akinetic mute	87.5	7.46	18.9	33
S	75	M	Midbrain & L. hemisphere	86.1	7.48	20.2	30
T	68	M	L. hemiplegia; R. hemiparesis	93.5	7.36	19.6	41
U	68	F	R. hemiplegia; bilat. signs	95.8	7.51	19.8	31
V	72	M	Bilat. hemiparesis	93.9	7.45	22.5	38
W	74	M	L. hemiplegia; R. hemiparesis	93.2	7.49	18.3	34
X	85	F	Bilat. hemiparesis	91.3	7.45	18.6	31
Y	56	M	R. hemiplegia	84.0	7.51	22.5	31
Mean				90.7±4.3	7.46±0.049	20.1±1.4	34.0±4.9

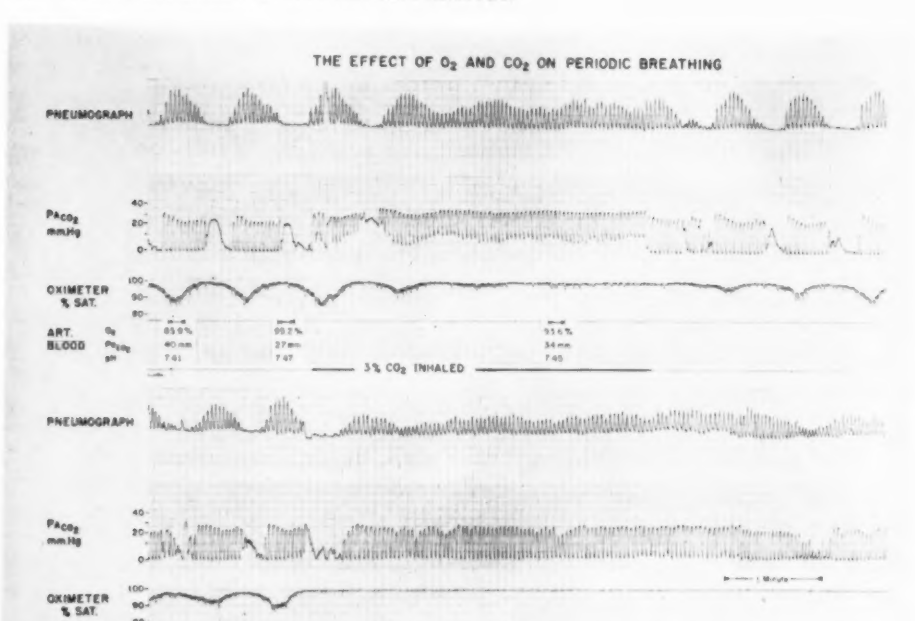


Fig. 5.—Studies on Case 6 (Table 4). Note that periodic breathing disappeared more promptly with CO_2 stimulation than it did after correction of anoxemia. Similarly, Cheyne-Stokes respiration more promptly reappeared when CO_2 stimulation was removed. The arterial blood values were obtained by direct analysis, since infrared alveolar air analysis ($PACO_2$) and oximeter readings give only approximate figures.

therapeutically, therefore, tends to correct the blood gas abnormality in the other which predisposes to phasic respiration.

Comment

The clinical and pathological findings in patients showing central hyperventilation all indicate that the respiratory abnormality is a response to medial pontile damage. The specificity of pontile lesions in producing central hyperventilation is implied by the lack of comparable abnormalities in either breathing patterns or respiratory blood gas contents among patients with vascular lesions elsewhere in the brain.

Although hyperventilation associated with pontile lesions is most easily explained by assuming that it is directly neurogenic, evidence to support this assumption is still incomplete. In other words, it is possible that deep brain stem damage may induce pulmonary and circulatory changes, which, in turn, stimulate the respiration. Such an indirect mechanism might explain the impermanence of hyperventilation in these subjects.

Anoxemia and metabolic acidosis were eliminated as causes of hyperventilation by the blood studies. (The arterial pH must fall to approximately 7.20 before respiration is stimulated by acidosis.[13]) Bronchopneumonia of the degree found in these patients does not ordinarily produce marked hyperpnea unless anoxemia is also present. Subclinical congestive heart failure and impaired circulation through the lower brain stem are two other potential causes of hyperpnea, which are more difficult to rule out.

The combination of a normal oxygen saturation and a decreased content of car-

bon dioxide in the arterial blood is also found in cardiac dyspnea.[14,15] In this latter state, hyperpnea may be present in the absence of an elevated systemic venous pressure.[16] The weight of evidence indicates that the dyspnea is primarily a symptom of pulmonary engorgement.[17] Harrison and his associates[18] demonstrated that both pulmonary and systemic venous congestion stimulate breathing through reflex mechanisms. When engorgement is produced experimentally in either the lungs or the inferior vena cava, the ventilation increases immediately. The respiratory response to both conditions is prevented by severance of the vagus nerves.

A specific pulmonary reaction occurring only with pontile lesions would have to be postulated if pulmonary congestion were the cause of central neurogenic hyperventilation. However, studies in experimental animals and humans indicate that neurogenic pulmonary edema is not a selective response to pontile lesions.[19-21] The autopsies on patients with central hyperventilation all showed at least some pulmonary congestion, but this was no more than is observed almost routinely in other severely ill, but nonhyperpneic patients. Also, Case 1 had no clinical evidence of any pulmonary congestion in spite of marked hyperventilation, and central hyperventilation has been observed clinically by others in young persons with brain stem lesions without evidence of heart or lung disease.[1,22] A final point against hyperventilation being secondary to pulmonary changes is that the breathing defect occasionally appeared simultaneously with the onset of the other neurological signs, and before any significant pulmonary changes had time to develop. All these reasons make it improbable that congestion of the lungs was responsible for the hyperventilation.

Reduced blood flow through the respiratory centers is another possible explanation for central hyperventilation accompanying pontine lesions. Schmidt[23] demonstrated experimentally that when the cerebral blood flow is reduced, respiration increases, and vice versa. Schmidt's observations were made during acute experiments. Data on the respiratory effects of a chronic reduction in cerebral blood flow are fragmentary and require inference. Three of the patients with cerebral vascular disease studied by Shenkin et al.[24] had cerebral blood flows reduced to below 35 cc/100 gm/min. No comment was made of any respiratory abnormality, but all three were hyperventilated, as indicated by markedly lowered arterial carbon dioxide contents. Data on the systemic circulation in these subjects were not given, but jugular venous carbon dioxide contents were below normal. With a low jugular CO_2 content, capillary stasis producing an elevated pCO_2 at the respiratory centers could not be inferred. Therefore, the reduced cerebral blood flow may have been significant in causing the hyperventilation. Descriptions of the brain lesions in these patients were not supplied.

Another illness in which hyperventilation with respiratory alkalosis is often seen is hepatic coma.[25] Indeed, the clinical picture of both the respiratory pattern and the neurological abnormalities in severe hepatic coma is similar to that seen in our cases of basilar artery thrombosis with central hyperventilation. The cerebral blood flow is depressed consistently[26] in the coma of liver disease. However, there is no present evidence as to whether the reduced cerebral blood flow is the cause or the result of the hyperventilation.

It is evident that circulation to the brain stem is impaired in patients with basilar artery thrombosis. The increased intracranial pressure and brain displacement which occur in patients with cerebral hemorrhages probably produce the same effect. On the other hand, there is nothing to suggest that the cerebral blood flow is reduced after anoxia or in encephalitis, although hyperventilation is seen in both these states. Also, basilar artery disease producing lesions outside the medial pons has not been found to produce manifest hyperventilation. Reduced cerebral blood flow may explain some instances of central

neurogenic hyperventilation, but it does not appear to be the cause in every case. Whether secondary to circulatory change or not, there must still be increased central neural activity to produce hyperpnea, and our present view is that this increased activity is supramedullary rather than directly medullary in origin. In spite of the marked facilitation of both inspiration and expiration in central hyperventilation, the respiratory centers retain their rhythmicity and their sensitivity to additional respiratory stimuli of both chemical and reflex origin. This pattern differs markedly from that seen with medullary respiratory failure, where early impairment of rhythmicity (Fig. 1) is followed by progressive insensitivity to chemical stimuli and, subsequently, unresponsiveness to reflex stimulation.[27]

Full counterparts to the prolonged, intense hyperventilation found in humans with pontile lesions have not been found in reports of work on respiratory neurogenesis in animals. In acute experiments in cats with midpontile transections,[28] normal respiratory patterns and normal arterial blood gas values were maintained. Apneusis, which bears no apparent physiological similarity to central hyperventilation, was associated with progressive respiratory acidosis. Although respiratory acceleration is produced in cats by stimulation of the dorsolateral pontile reticular formation,[29] blood gas studies on such preparations are presently lacking. Ngai and Wang did observe "marked hyperpnea and tachypnea" during the course of electrolysis of these dorsolateral pontile areas. The same workers found no definite respiratory changes when they placed relatively large electrolytic lesions medially in the pontile reticular formation. In acute experiments in our own laboratory, the placement of discrete electrolytic lesions in this area of the medial pontile tegmentum has also failed to produce significant respiratory alterations.

Formulation of the exact neurogenesis of central hyperventilation is still tentative, both because of the lack of experimental counterparts to the human respiratory abnormality and because of the caution required in drawing physiological inferences from human pathological material. There was a considerable similarity between the anatomy of the pontile necrosis in Cases 4, 5, 6, and 9 with central hyperventilation and the anatomy of lesions associated with decerebrate rigidity in both humans[30] and experimental animals.[31] The fact that central hyperventilation sometimes developed in the absence of spasticity of the extremities excluded the concept that the hyperpnea was merely a decerebrate rigidity of respiration. Nevertheless, both the clinical and the pathological studies demonstrated a close relationship between the neural mechanisms facilitating respiration and the mechanisms facilitating reflex tonus in skeletal muscle. Structures in the medial pons must be regarded as at least indirectly inhibitory to respiration, therefore, and it is our surmise that the critical areas lie in the medial pontile reticular formation.

It is our hypothesis that central neurogenic hyperventilation in man results from the uninhibited stimulation of both the inspiratory and expiratory centers in the medulla by the lateral pontile reticular formation and by laterally located descending neural pathways. It is possible that this stimulation operates primarily through central facilitation of afferent respiratory reflexes coming from the vagus and from somatic sensory pathways.

We are not yet certain whether or not less severe degrees of neurogenic hyperventilation result from suprapontile lesions in man. A recent communication concludes that patients with bilateral disease of the cerebral hemispheres show both a moderate neurogenic hyperventilation and an exaggerated respiratory response to physiological stimuli.[32] Our reasons for not drawing such conclusions from our own data are indicated above. It is well known, however, that most patients with Cheyne-Stokes respiration are hyperventilated with respect to carbon dioxide.[33] Evidence to date is not sufficient to determine whether

this stimulation invariably has its origin in cardiopulmonary defects or whether neurogenic factors may at times provide the necessary impetus. The greatly increased frequency of Cheyne-Stokes breathing in patients with bilateral cerebral or brain stem disease favors the assumption that at least some cases of periodic respiration have a direct neurogenic component.

Summary

Quantitative analyses of the respiration in nine patients with acute brain stem disease demonstrated a true, and apparently neurogenic, hyperventilation. Minute alveolar ventilations were increased from one and one-half to four times the normal resting level, and there was a profound hypocapnia with arterial alkalosis but no anoxemia. The respiratory responses to reflex and chemical stimuli were preserved. Clinical observations indicated severe dysfunction of medially placed pontile structures. Autopsies demonstrated medial pontile destruction in five subjects, with indirect damage to this area in a sixth. Extraneural abnormalities were insufficient to explain fully the respiratory change.

Control studies on 25 patients with acute vascular lesions of the hemispheres or the brain stem outside the pons showed mild to moderate reductions in $PaCO_2$ in several. These mild abnormalities were interpreted to be the results of moderate cardiopulmonary abnormalities which almost universally accompany cerebral vascular disease. There was almost no overlap between the $PaCO_2$ values obtained in the controls and those obtained in the pontile group.

It is our hypothesis that structures in the medial pontile reticular formation of man are at least indirectly inhibitory to respiration. Central neurogenic hyperventilation would thus result from the uninhibited stimulation of the medullary respiratory centers by the lateral pontile reticular formation and laterally placed descending neural pathways. This stimulation may act primarily through the central facilitation of afferent respiratory reflexes coming from the vagus and from somatic sensory pathways.

Mrs. Betty McGowan and Mr. Charles Donaldson gave technical assistance. Dr. Raymond Hain assisted us in the preparation and interpretation of the pathological material.

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Appendix

CASE 1.—A 39-year-old woman was comatose, flaccid, and breathing quietly after removal from a gas-filled room. Twenty-four hours later bilateral decerebrate rigidity and hyperventilation were observed. The blood pressure was 120/70 mm. Hg; lungs were clear. The following day both spasticity and respiratory abnormalities were absent, and she began to arouse. She recovered, with no neurological residua. The clinical diagnosis was anoxic anoxia of the brain.

CASE 2.—A 45-year-old man had an acute right cerebral hemorrhage. His blood pressure was 180/100 mm. Hg, and he was conscious but had left hemiplegia. A chest x-ray showed clear lungs and an enlarged heart. Two days later he suddenly lost consciousness and developed opisthotonos and hyperventilation. The pupils were constricted; the jaws were clamped shut, and there was bilateral decerebrate rigidity, more pronounced on the left than on the right. The lungs were clinically clear except for expiratory rhonchi. Death occurred 24 hours later. Autopsy showed a large right cerebral hemorrhage with brain-stem compression, particularly of the pons. The heart was moderately enlarged and weighed 450 gm. There was old fibrosis of the left ventricular wall. The combined weight of the lungs was 870 gm., and section revealed a moderate degree of posterior pulmonary congestion. The kidneys were unremarkable.

CASE 3.—A 53-year-old man suddenly collapsed, unconscious. The blood pressure was 180/100 mm. Hg, and breathing alternated between hyperventilation and Cheyne-Stokes respiration. He had a stiff neck and left hemiplegia with bilaterally increased stretch reflexes and a bilateral Babinski sign. The lungs were originally clear, but basal rales later developed. The spinal fluid was bloody,

Two days later he had sustained hyperventilation, skew deviation of the eyes, and alternating periods of bilateral decerebrate rigidity and diffuse flaccidity. Hyperventilation persisted for a week, and respiratory studies (Table 1) showed similar changes on the third and eighth hospital days. He died on the 10th day. At autopsy, a ruptured aneurysm was found on the anterior communicating artery. The resultant cerebral hemorrhage had produced midbrain compression and extensive hemorrhages of the central pons and midbrain. The heart and kidneys were normal. The lungs combined weighed 1,450 gm. and presented bronchopneumonia and pulmonary edema.

Case 4.—A 56-year-old man had diabetes for eight years and a blood pressure of 180/90 mm. Hg one year before admission. He was admitted with generalized weakness and vomiting. During his first 24 hours in the hospital left hemiplegia developed. Cheyne-Stokes respiration was present. The following day he was comatose, had a skew deviation of the eyes, and was flaccid. Rales were noted at both lung bases. The BUN was 74 mg. %. Hyperventilation was observed 2 days after admission and again 24 days after admission. He died on the 26th day. Autopsy showed a thrombus in the midportion of the basilar artery with infarction of the central pons and midbrain and in the right cerebral hemisphere. The heart was moderately enlarged, and there were old occlusions of the right and left coronary arteries, with an acute left anterior myocardial infarct. The lungs showed only moderate posterior hyperemia and edema. There were bilateral nephrosclerosis and agonal hemorrhagic duodenitis.

Case 5.—A 57-year-old man suddenly lost consciousness. The blood pressure was 122/78 mm. Hg, and the patient was comatose and had hyperventilation on admission. There were bilateral trismus and extensor rigidity, more pronounced on the left than on the right. The eyes were directed straight ahead, the right pupil being larger than the left. The chest x-ray showed clear lung fields; clinical examination showed only scattered chest rhonchi. The BUN was 14 mg. %. By the fourth day the neurological picture changed to diffuse flaccidity, but hyperventilation remained. His body temperature dropped to 93 F. Bronchopneumonia developed, but he survived five more days.

Autopsy showed a fresh thrombus occluding the basilar artery from just above the origin of the superior cerebellar arteries to its rostral end. There was central necrosis of the pons, extending up through the midbrain and into the left thalamus. The heart was normal except for minimal coronary atherosclerosis. The lungs showed a confluent bronchopneumonia and posterior congestion. Aside from an acute hemorrhagic duodenitis, the rest of the examination, which included the kidneys, was noncontributory.

Case 6.—A 69-year-old man had symptoms of intermittent basilar insufficiency for six weeks. For 24 hours he was drowsy and showed diffuse weakness. On admission he was obtunded but responded to simple commands. He had Cheyne-Stokes breathing; the extremities were bilaterally paretic particularly on the right, and the Babinski sign was elicited bilaterally. The blood pressure was 140/75 mm. Hg; the lungs were clear. Three days later he became unresponsive and showed central hyperventilation. Spasticity failed to develop, although stretch reflexes were bilaterally increased. There was a skew deviation of the eyes with an anterior internuclear ophthalmoplegia. Examination of the lungs showed diffuse rales posteriorly. A chest x-ray was unsatisfactory. The BUN was 26 mg. %. He died eight hours after study.

At autopsy the left vertebral artery was found to be thrombosed and the basilar artery severely calcified and partially occluded. Scattered small areas of fresh necrosis were found in the central portions of the rostral pons, midbrain, and thalamus. The heart weighed 520 gm. and showed moderate coronary atherosclerosis without occlusion. There was passive congestion of the liver. The lungs were well aerated but weighed 1,260 gm. combined and showed posterior congestion. The kidneys showed moderate hyalinization of the renal arterioles with occasional fibrosed glomeruli.

Case 7.—A 70-year-old man suddenly became stuporous. He had Cheyne-Stokes respiration, a bilateral anterior internuclear ophthalmoplegia, and bilateral spasticity with increased reflexes and Babinski sign. The following day he developed central hyperventilation, became comatose, and was bilaterally decerebrate. The blood pressure was 120/80 mm. Hg. The chest was clear, although an x-ray showed an old pneumoconiosis. The venous pressure was 180 mm.; the circulation time (arm to tongue), 15 seconds, and the electrocardiogram showed a left bundle-branch block. The BUN was 14 mg. %. He lived a week following respiratory studies, during which time he developed bronchopneumonia. Permission for autopsy was refused. The clinical diagnosis was basilar artery thrombosis with pontile infarction.

Case 8.—A 77-year-old woman had intermittent vomiting for two weeks, slurred speech for one day, and sudden collapse on the day of admission. She had Cheyne-Stokes breathing, was stuporous, and had an anterior internuclear ophthalmoplegia. There was moderate spasticity bilaterally, with the Babinski sign. The following day she became comatose and developed central hyperventilation and bilateral decerebrate rigidity. Her blood pressure was 140/90 mm. Hg. The heart was unremarkable. The lungs were clear on physical examination, and

a chest x-ray showed only an enlarged left ventricle and negative lung fields. Subsequently she developed bronchopneumonia and died. The clinical diagnosis was basilar artery thrombosis with ventile infarction. Permission for autopsy was refused.

CASE 9.—A 82-year-old man was found at home "breathing heavily and unable to talk." On admission he was stuporous and anarthric and had periodic breathing. Later he became unresponsive, showed an anterior internuclear ophthalmoplegia, and had a flaccid left and spastic right hemiplegia. There were bilateral decerebrate responses to pain, however, and a bilateral Babinski sign. Respirations varied between central hyperventilation and periodic breathing. The blood pressure was 120/80 mm. Hg. The lungs were clear save for scattered coarse rhonchi, and there was auricular fibrillation. The BUN was 40 mg. %. He was digitalized on admission, and respiratory studies were done 48 hours later, during a period of hyperventilation. Subsequently he developed clinical signs of pulmonary congestion and pneumonia and died on the 18th hospital day. At autopsy the brain showed a fresh embolus of the midportion of the basilar artery. There was necrosis of the central pons (Fig. 3), but the remainder of the brain was remarkably well preserved in view of the patient's age. The combined weight of the lungs was 1,480 gm., and there were bilateral acute pulmonary emboli with pulmonary infarction. Diffuse acute posterior bronchopneumonia and congestion were found. The heart showed minimal atherosclerosis, and there was an acute mesenteric thrombosis with hemorrhagic infarction of the small intestine.

Effect of Lidocaine (Xylocaine) on Seizure and Interseizure Electroencephalograms in Epileptics

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Local anesthetics in moderate doses have a blocking action not only on peripheral nerve fibers but on nervous structures in general.[1] That they produce an anticonvulsive effect too has been demonstrated in recent years by Bernhard and Bohm.[2] These authors studied in animals the inhibitory effect of local anesthetics on poststimulatory cortical after-discharge.[3] Clinically the anticonvulsive effect was observed in status epilepticus of mainly focal type.[4] It was further established that cortical discharges in certain types of epilepsy produced by intermittent photic stimulation were blocked by lidocaine.[5] Experimental studies on animals indicated that lidocaine was decidedly superior to other local anesthetics,[3] and since, moreover, Clive-Lowe and associates[7] (1954) demonstrated, in a large clinical series, that lidocaine could be given intravenously in moderate doses without danger of toxic reactions, recent clinical investigations in this field have been chiefly concerned with this drug. In 1957, however, French et al.[8] reported superiority of procaine in an experimental investigation on animals that incidentally confirmed Bernhard and Bohm's observations on the anticonvulsive effect of local anesthetics.

The cerebral activity has not been recorded previously in connection with the arrest of "spontaneous" epileptic seizures with lidocaine. Nor has electroencephalography been utilized for studying the effect of lidocaine on different types of interseizure activity in epileptics. These problems will be considered in this paper.

Nomenclature and Methods

Lidocaine (Xylocaine; α-diethylamino-2,6-acetoxylidid) hydrochloride* was given intravenously in 2% solution with an injection rate of 2 cc. (40 mg.) per minute up to a total amount equivalent to 2-3 mg. per kilogram of body weight. For arresting spontaneous seizures lidocaine was injected somewhat faster, as indicated below.

As a rule, anticonvulsants had been withdrawn one or two days before examination at the electroencephalography laboratory.

Electroencephalograms were recorded with a six- or eight-channel Grass apparatus. Bipolar recording was employed, with 21 electrodes placed as described by Penfield and Jasper.[9] Conventional longitudinal and transverse leads were used.

Classification of the electroencephalograms was based, with slight modifications, on the scheme reported by Buchthal and Lennox.[10] Electroencephalograms with essentially 8-13/sec. waves were classed as normal. "Slight nonparoxysmal abnormality" referred to a moderate amount (more than 15%) of 5-7/sec. waves with amplitudes equal to or greater than those of the basic activity. "Pronounced nonparoxysmal abnormality" implied, in addition, a certain amount of slower waves. "Paroxysmal" meant an abnormality with groups of waves having lower frequencies than those of the basic activity and with amplitude rising to more than twice that of the basic discharges. Paroxysmal abnormality also included spikes and sharp waves.

Material

Our series consists of 31 epileptics (16 female and 15 male subjects) who were referred in 1957, as out- or inpatients, to the neurophysiology labo-

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*Lidocaine (Xylocaine) hydrochloride, manufactured by Astra Pharmaceutical Products, Inc., Worcester, Mass.

ratory at Sahlgrenska sjukhuset, Gothenburg, for electroencephalographic examination. The types of epilepsy are evident from the following case reports. Two patients were aged 11-20 years; 18, 21-40 years, and 11, 41-60 years.

Results

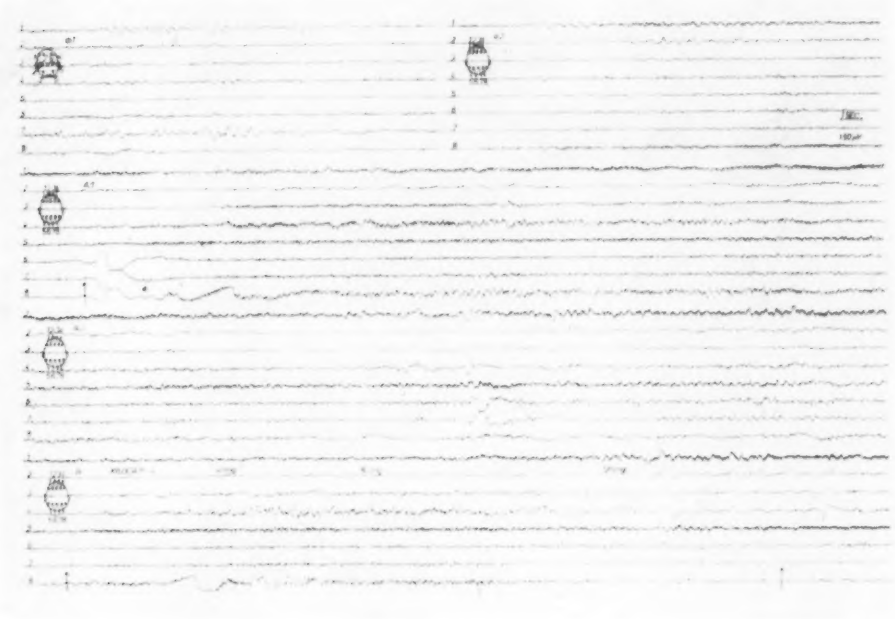
Effect of Lidocaine on Status Epilepticus of Focal Type

In three cases with status epilepticus of focal type we administered lidocaine during electroencephalographic recording.

CASE 1.—A woman, aged 51, with grand mal and right-sided focal symptoms of 10 years' standing, was admitted in status epilepticus. Left carotid angiography was normal. The seizures, occurring at 5-10-minute intervals and lasting about three minutes, were of very uniform nature, with initial crying, rotation of the head to the right, tonic and clonic spasms in the right arm and leg, and slight disturbance of consciousness. Figure 1, top, shows the interseizure EEG; there is a marked left frontotemporal abnormality. The next group of tracings record a spontaneous seizure, the onset of which was marked by rotation of the head to the right (arrow to the left). At the onset there was approximately 10/sec. activity with amplitudes greater than those of the basic activity; on the right side, there are some motion artifacts. After 30-40 seconds bilaterally synchronous 3-5/sec. activity appeared, interspersed with some sharp waves, which were for the most part left temporal (*A1:2*). The seizure activity and the clinical seizure subsided after three minutes. A needle was then inserted for intravenous injection, and, at the onset of the next spontaneous seizure, 120 mg. of lidocaine hydrochloride was injected within the course of 25 seconds. After about 30 seconds, approximating the circulation time from arm to brain, the seizure terminated within a few seconds. This seizure recording is shown in Figure 1. The activity was similar to that in the previous seizure, although the frequency of paroxysmal discharges was substantially less. On termination of the seizure, the EEG returned to its initial appearance. Subsequently the patient was free of seizures for 50 minutes, but then had an abortive seizure with electroencephalographic changes for 10 seconds. Thereafter there were no further seizures for a considerable time.

The electroencephalographic picture here is of special interest, since arrest of seizures with lidocaine during EEG recording has not previously been described in the literature.

Fig. 1.—Woman, aged 52, with status epilepticus of focal type.
a:1-a:2: Interseizure EEG. *A:1-A:2:* Seizure EEG. *B:* Seizure arrested by lidocaine intravenously.



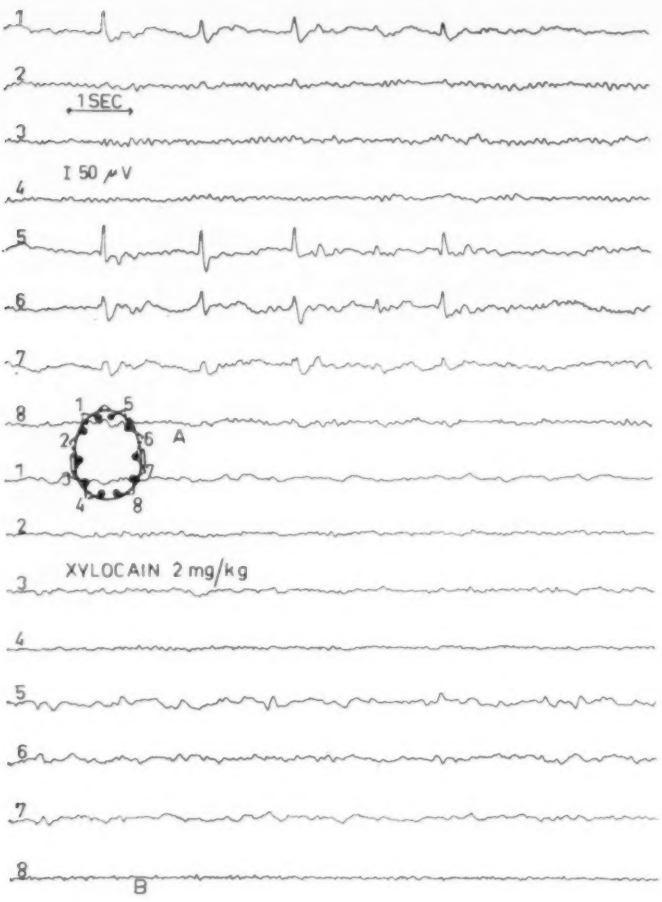


Fig. 2.—Man, aged 60, with grand mal.

A (before lidocaine): Sharp waves occur in right frontotemporal region. *B* (after lidocaine): Sharp waves are scarcely detectable.

We have observed a similar effect of lidocaine intravenously in the same doses on a further two cases of focal status epilepticus.

Effect of Lidocaine on Various Types of Interseizure Activity

1. Focal Abnormality of Epileptogenic Type.—In 20 cases we studied the effect of lidocaine on focal epileptogenic abnormality. The results are illustrated by typical cases.

CASE 2.—A man, aged 60, with hypertension of several years' standing, was admitted after focal epileptic seizures indicating involvement of the right hemisphere. The EEG (Fig. 2*A*) showed focal sharp waves from anterior leads over the right hemisphere. After injection of 2 mg. of lidocaine hydrochloride per kilogram of body weight, the sharp waves either disappeared or were scarcely detectable (Fig. 2*B*).

We have observed a similar effect of lidocaine in a further 10 cases of this type. In one case, however, lidocaine hydrochloride in a dose of 120 mg. (2 mg. per kilogram) had no effect on the focal sharp-wave activity.

CASE 3.—A woman, aged 33, had had grand mal seizures since the age of 20, as well as attacks of ambulatory automatism and somnambulism. In the last few years there had been sporadic brief lapses of consciousness, with slight motor activity but no focal signs. Neurologic examination was normal. The resting EEG (Fig. 3*A*) revealed sharp waves from the right frontotemporal region, together with 2-4/sec. waves from the right frontotemporal and parietal zones. Lidocaine hydrochloride was given intravenously in a total dose of 200 mg., or 3 mg. per kilogram of body weight.

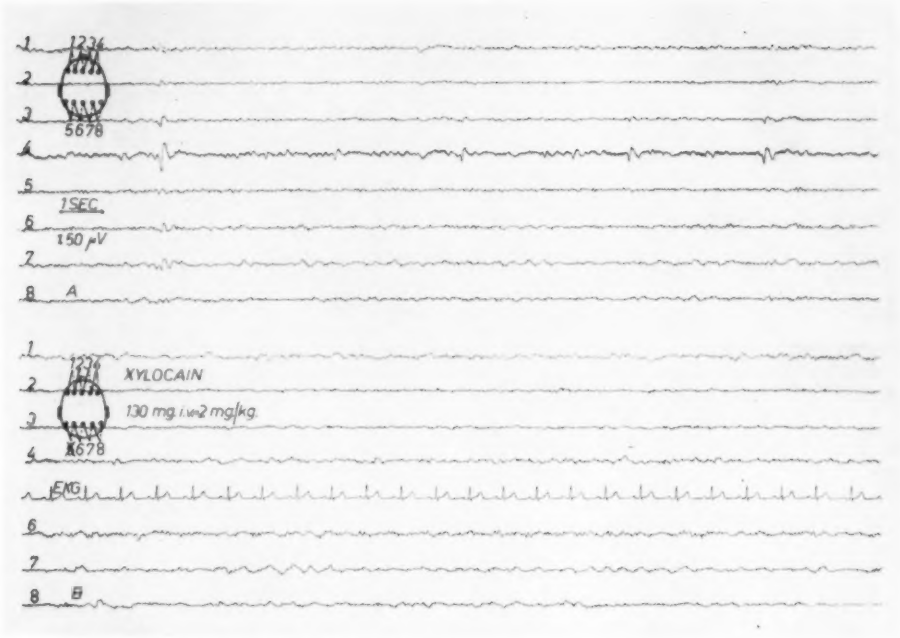


Fig. 3.—Woman, aged 33, with grand mal.
A (before lidocaine): Sharp waves in right frontotemporal region; slow waves in right frontotemporal and parietal regions. *B* (after lidocaine): Sharp waves disappear, but the slow ones in the parietotemporal region increase (electrocardiogram irrelevant here).

With 130 mg. (2 mg. per kilogram) the sharp waves from the frontotemporal region disappeared. Concurrently, however, there was a substantial increase in the slow waves from the parietotemporal region on the same side (Fig. 3*B*). (The electrocardiogram in this Figure is irrelevant here.)

In an additional six cases we found that lidocaine had a dampening effect on the sharp waves in anterior leads, coincident with an increase in the number of slow waves in posterior leads.

Two more patients with epileptic seizures of focal type showed interseizure activity consisting of sharp waves that were not focal, but were referable to large parts of both hemispheres, and which shifted from side to side. In these two cases we found no dampening effect on the sharp waves by the injection of lidocaine.

II. Bilaterally Synchronous Activity of Epileptogenic Type.—Five patients had petit mal seizures; three of them also had more or less frequent grand mal seizures without focal signs. In these cases the EEG revealed typical bursts of 3/sec. wave-and-spike activity; simultaneously, with the electroencephalographic examination we administered lidocaine hydrochloride intravenously, in a dose of up to about 2 mg. per kilogram of body weight. The effect of the injection varied very greatly. Two patients showed the typical 3/sec. wave-and-spike complexes in less frequent episodes after the injection of lidocaine. In another case episodes occurred more frequently after the injection. In yet another patient we observed no difference at all after the injection. In the fifth case episodes of 3/sec. wave-and-spike activity were equally frequent after the injection, but the amplitude of the slow waves had decreased and the spike component was of longer duration and coarser in appearance.

In another patient, however, lidocaine produced a remarkable and unequivocal

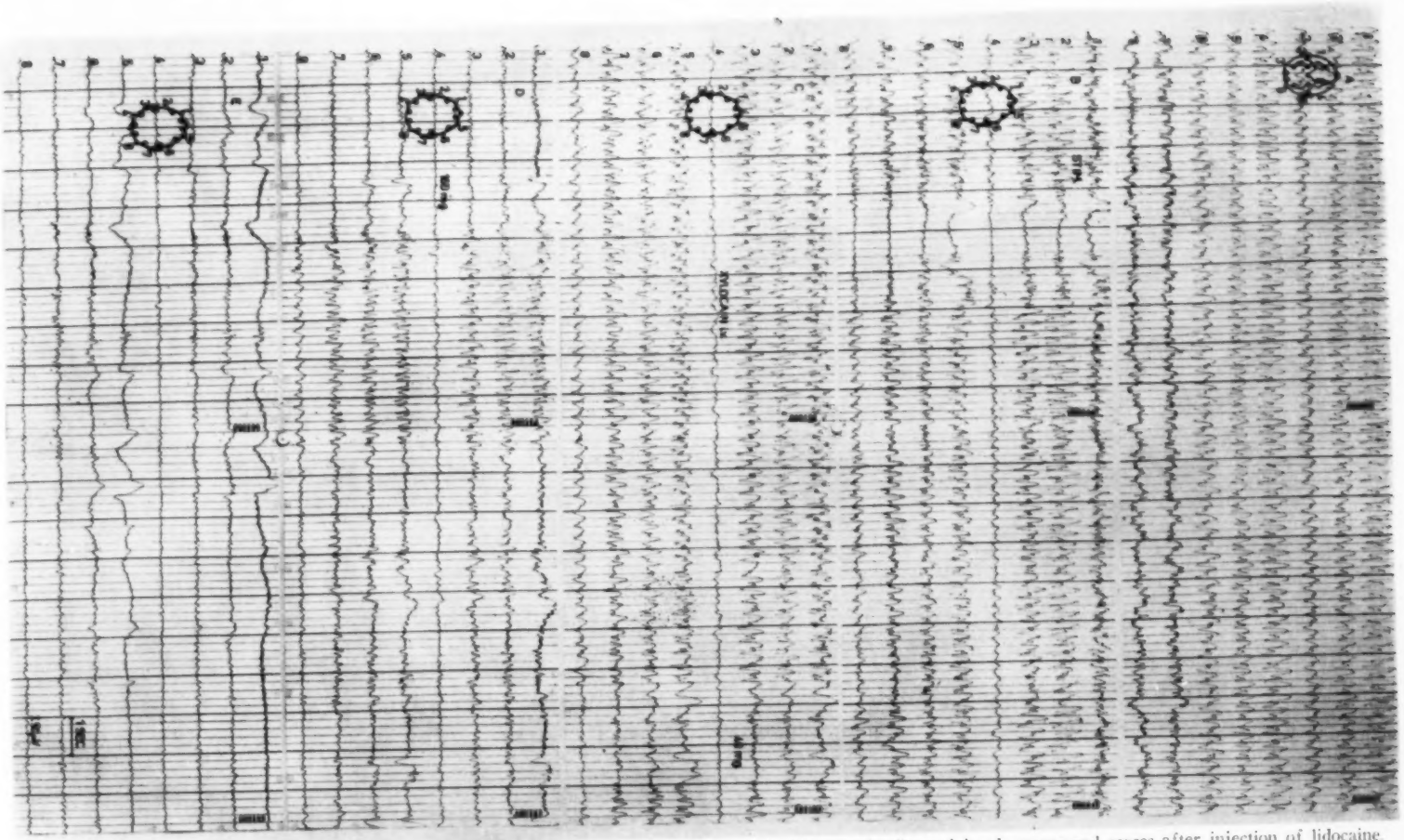


Fig. 4.—Man, aged 24, with petit mal status. *A* and *B*: Before injection of lidocaine. *C-E*: Wave-and-spike activity decreases and ceases after injection of lidocaine.

effect. This was one of the unusual cases with petit mal status.

CASE 4.—A 24-year-old man had suffered from petit mal seizures since the age of 8 years. He had long refused adequate therapy but took homeopathic pills. The day before electroencephalographic examination he had suffered a grand mal seizure, followed by a period with several petit mal convulsions per minute. The EEG showed continuous 3/sec. wave-and-spike activity symmetrically over both hemispheres (Fig. 4). A needle for intravenous injection was introduced into an arm vein. The electroencephalographic tracing was not influenced either by this manipulation or by injection of isotonic sodium chloride solution. Following this, 160 mg. of lidocaine hydrochloride was injected; about 30 seconds later the epileptogenic abnormality disappeared and the petit mal status ceased.

Aside from the foregoing cases, the effect of lidocaine was studied in five cases with epileptic manifestations in which resting electroencephalograms had shown largely nonspecific discharges with occasional sharp waves or other paroxysmal activity. In two of these cases with pronounced electroencephalographic changes, lidocaine was followed by an increased number of low-frequency waves. In two cases with relatively slight changes, lidocaine produced no conspicuous alteration. In one case the paroxysmal discharges were reduced.

Comment

It has been shown [4] that epileptic seizures of grand mal type, with or without focal signs, can be arrested by intravenous injection of lidocaine. We have been able to confirm this and to illustrate it electroencephalographically. The dose of lidocaine that may abolish the seizure discharges in status epilepticus is low. In our cases scarcely more than 20 to 40 mg. could have reached the cerebral vessels when the seizures terminated and the preictal activity was restored. This contrasts with the substantially higher doses of lidocaine that were required for reducing focal interseizure activity in those cases in which it occurred (even the opposite effect has been observed). The question arises whether the epileptic seizure itself is not associated with such alterations in the central nervous environment as to promote the anticonvulsive action of lidocaine. It may be possible that in an epileptic seizure the blood-brain barrier so changes that lidocaine can reach the nervous tissue faster and in a higher concentration.

In regard to the effect of lidocaine on interseizure discharges, it is difficult to draw any definite conclusions regarding the point of attack of the drug.

In some groups, such as, for instance, those with bilaterally synchronous epileptogenic activity consisting of typical or atypical wave-and-spike complexes, the effect varied greatly. In some patients the abnormal activity decreased; in others it was unaffected; in others, again, it increased. The manipulations required in activation naturally may affect the patient's degree of alertness and accordingly influence the electroencephalogram. In order to reduce this factor, the injection needle was therefore inserted into the vein 10 to 15 minutes before injection. In the examination of human subjects it is impossible, however, completely to eliminate all of those stimuli that may influence the EEG, particularly the bilaterally synchronous types of abnormality, which are so sensitive to different stimuli. The more an abnormality varies "spontaneously," the more difficult will it be to evaluate the effect of a drug. Hence we would not venture to draw from our series any conclusions regarding the effect of lidocaine on bilaterally synchronous electroencephalographic changes.

In one special group we found, however, a more uniform effect of lidocaine. These cases had sharp waves of distinct type with a short initial phase and circumscribed localization, and it was precisely here that the sharp-wave activity decreased after injection of lidocaine. This possibly suggests that a point of attack for lidocaine exists at cortical level.

In several cases with focal sharp waves, slow waves, too, were recorded within their range of distribution. After injection of

lidocaine it was often found that, coincident with a decrease or disappearance of sharp waves, the slow waves were more profuse and of larger amplitude. Sometimes, moreover, slow waves also appeared in a region where they had not previously been recorded. It is not clear whether this abnormal activity results from excitation or constitutes a release phenomenon, as, for instance, when latent focal changes are manifested during narcotic activation, or whether entirely different factors, such as altered circulatory conditions, give rise to it. A further consideration lies in Walter's [11] (1938) suggestion that "slow waves serve the purpose of ensuring constancy of neuronal environment" (quoted by Cobb,[6] 1957). On this theory, the slow waves that we observed coincident with the disappearance of sharp waves after injection of lidocaine would constitute not a fresh abnormality but a phase of the process that occurs when lidocaine inhibits this epileptogenic activity.

Summary

In three cases of status epilepticus with seizures of focal type, the seizures were arrested by lidocaine (Xylocaine) hydrochloride administered intravenously during recording of electroencephalograms.

In 28 additional cases of epilepsy the effect of lidocaine on the interseizure activity was studied electroencephalographically.

In focal abnormality the sharp-wave components often decreased or disappeared, but slow waves were more profuse and of larger amplitude within the same focus. In a few cases it was observed that, coincident with the disappearance of focal sharp waves, slow waves appeared in a more posterior region of the same hemisphere.

The effect of lidocaine on bilaterally synchronous paroxysmal abnormality varied greatly, though in one case of petit mal status it was prompt and lasting.

Sahlgrenska sjukhuset (Dr. Petersén).

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Penicillin Treatment of General Paresis (Dementia Paralytica)

Results of Treatment in 1,086 Patients the Majority of Whom Were Followed for More Than Five Years

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Introduction

This paper is a cooperative report of the clinical, spinal fluid, and serologic findings in a group of 1,086 patients with general paresis (dementia paralytica) treated with penicillin with or without fever therapy at eight different hospitals. A detailed account of the formation and function of this cooperative clinical study has been given previously as an introduction to the presentation of the group experience in treatment of asymptomatic central nervous system syphilis.[1]

Shortly after the effectiveness of penicillin in the treatment of early syphilis was reported, various investigators began to study the efficacy of this new antibiotic in the treatment of central nervous system syphilis. These investigations were supported in part by grants from the Office of Scientific Research and Development, the National Institutes of Health, and the Division of Venereal Disease, U. S. Public Health Service. The findings of the individual investigators have provided much of the background information which is the basis for current therapeutic practices in treatment of general paresis.

As the effectiveness of penicillin treatment became apparent, it was realized that, in order to provide a definite basis for management of general paresis, it would be necessary at some time to pool the experience of clinicians in the same fashion as was done by the Cooperative Clinical Group in evaluating metal chemotherapy in all stages of syphilis. Therefore, the clinical experience of the individual investigators was pooled to provide statistically significant numbers of patients, (1) who represented the multiplicity of clinical manifestations of general paresis, (2) who were subjected to a variety of methods of treatment with the two modalities under consideration, and (3) who were followed for sufficient time periods.

The participating hospitals were as follows: Boston Psychopathic Hospital, 367 patients; St. Elizabeths Hospital, 188 patients; University of Michigan Hospital, 133 patients; University of Pennsylvania Hospital, 129 patients; The Johns Hopkins

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This study was supported in part by research grants from the National Institutes of Health, U. S. Public Health Service, Bethesda, Md.

The Johns Hopkins Hospital (Drs. Hahn and Moore†); New York Hospital (Dr. Webster); St. Elizabeths Hospital (now with Veterans Administration) (Dr. Weichhardt); Bellevue Hospital (Dr. Thomas); Boston Psychopathic Hospital (Drs. Timberlake and Solomon); University of Pennsylvania School of Medicine (Drs. Stokes and Gammon); Emory University School of Medicine (Dr. Heyman) (now at Duke University); Statistician, U. S. Public Health Service (Mrs. Gleeson); University of Michigan Medical School (Dr. Curtis); Assistant Surgeon-General, U. S. Public Health Service (Dr. Cutler).

† Dr. Moore died Dec. 6, 1957.

Hospital, 80 patients; Bellevue Hospital, 67 patients; Grady Memorial Hospital, 68 patients, and New York Hospital, 54 patients.

Method of Study

A committee representing each of the cooperating institutions planned the study and assumed responsibility for continuing consultation and supervision. A subcommittee * was appointed to work out in detail the method for collecting and processing the data.

To be able to pool information, it was necessary to agree upon definitions of the disease to be studied, as well as a uniform method of recording signs, symptoms, and laboratory findings by which the status at time of diagnosis, treatment, and follow-up could be indicated. Finally, uniform data collection sheets had to be devised, given preliminary testing by each collaborating clinic, revised as found necessary in preliminary trials, and then placed in the clinics for use. Before final coding, clinical and statistical representatives jointly visited each collaborating clinic to review with the abstracting staff the data collection sheets in order to assure uniformity of the abstracting process by the clinical staff in each institution. In this way, similar handling of clinical and laboratory data was assured. A continuing, close working relationship between the subcommittee and the associated clinics made possible what is believed to be a high degree of uniformity in interpreting and abstracting the records.

It is obvious to those familiar with general paresis that borderline cases exist, particularly those in which a strongly positive and active spinal fluid is accompanied by minimal or equivocal clinical evidence of disease. With the alcoholic or the aged person with positive laboratory findings in the blood and spinal fluid, the question enters as to the relationship between syphilitic infection and the paretic-like clinical findings, which might have a different etiology.

Since it is impossible, when comparing patients handled by different clinicians, even within the same clinic, to assure complete identity of criteria upon which a diagnosis is based, it was agreed that each clinic would be asked to enter patients on the basis of its diagnosis of general paresis. However, as seen by the reference to the section entitled "Type of Paretic Psychosis at Time Study Treatment Started" (Fig. 1A) of the abstracting sheet (Figs. 1A-1D), there was opportunity to indicate the basis for the diagnosis. Furthermore, objective and subjective evidence supporting the diagnosis was afforded by the listing of the clinical and laboratory findings shown in the section entitled "Serologic Examination" (Fig. 1C) and in the symptom list shown in Figure 1D.

Follow-up observations were made at intervals, when signs, symptoms, and laboratory findings were recorded (Figs. 1E and 1F).

Since both the stated diagnosis and the reported clinical and laboratory findings were used for analysis, it is felt that sufficient information is available to compensate in large part for differences in criteria of the various clinics. In considering laboratory findings, the levels of normality or significance of cell count or protein utilized were those set by the reporting unit. Changes after treatment were considered as showing either improvement or retrogression at each follow-up period.

In this cooperative effort, not all clinics used the same type of serologic test for syphilis. However, standardization of test procedures, antigens, or levels of sensitivity among clinics was considered unnecessary, since the individual clinics, for the most part, used the same testing techniques throughout the time period of the study and the serologic status of patients during post-treatment observation has been evaluated as improved, unchanged, or progressed in relation to status in the given clinic at time of treatment.

* Dr. Richard D. Hahn, The Johns Hopkins Hospital, Baltimore; Dr. John C. Cutler and Mrs. Geraldine Gleeson, U. S. Public Health Service.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE

MEDICAL ABSTRACT
COOPERATIVE NEUROSYPHILIS STUDY

BUDGET BUREAU NO. 68-S104.1
APPROVAL EXPIRES 2-28-54

PATIENT'S NAME (Last) (First)	PATIENT NO.
CLINIC	DATE PENICILLIN TREATMENT STARTED

Cases falling into one or more of the following categories are to be included in the Cooperative Neurosyphilis Study:

(a) Cases of Asymptomatic Neurosyphilis of at least 2 years' duration with abnormal spinal fluid and without diagnosable signs or symptoms *(as verified by opthalmoscopic and neurologic examination)*.

(b) Cases of Paresis and Taboparesis where there is evidence of psychotic brain damage by signs or symptoms, or where diagnosis has been made on the basis of somatic grounds alone *(defined as physical signs without psychosis)*.

(c) Cases of Primary Optic Atrophy *(hereafter referred to as POA)* where there are definite changes by opthalmoscopic, perimetric and/or corrected visual acuity tests *(two must be positive)*.

DIAGNOSIS AT TIME STUDY TREATMENT STARTED *(Circle one)*	
1.	ASYMPTOMATIC
2.	PARESIS ALONE
3.	TABOPARESIS ALONE
4.	PRIMARY OPTIC ATROPHY
5.	PARESIS WITH POA
6.	TABOPARESIS WITH POA

TYPE OF PARETIC PSYCHOSIS AT TIME STUDY TREATMENT STARTED *(Circle one)*			
0.	NO PARESIS	4.	MANIC-GRANDIOSE, EXPANSIVE
1.	SOMATIC GROUNDS ALONE	5.	DEPRESSED
2.	SIMPLE DEMENTED, DIAGNOSIS DEFINITE	6.	PARANOID
3.	SIMPLE DEMENTED, DIAGNOSIS QUESTIONABLE	9.	UNCLASSIFIED OR UNKNOWN

RACE AND SEX *(Circle one)*			
1.	WHITE MALE	4.	WHITE FEMALE
2.	COLORED MALE	5.	COLORED FEMALE
3.	OTHER MALE	6.	OTHER FEMALE

AGE *(In years)* AT TIME STUDY TREATMENT STARTED *(Circle one)*			
0.	0-9	5.	50-59
1.	10-19	6.	60-69
2.	20-29	7.	70-79
3.	30-39	8.	80 OR MORE
4.	40-49	9.	AGE UNKNOWN

WEIGHT IN KGS. AT TIME STUDY TREATMENT STARTED *(Circle one)*			
1.	UNDER 40 KGS.	6.	80-89
2.	40-49	7.	90-99
3.	50-59	8.	100 OR MORE
4.	60-69	9.	WEIGHT UNKNOWN
5.	70-79		

DURATION OF SYPHILIS INFECTION AT TIME OF STUDY TREATMENT *(Circle one)*			
0.	CONGENITAL	5.	20-24
1.	2-4 YEARS	6.	25-29
2.	5-9	7.	30-39
3.	10-14	8.	40 OR MORE
4.	15-19	9.	DURATION UNKNOWN

DURATION OF NEUROSYPH SYMPTOMS AT TIME STUDY TREAT STARTED *(Circle one)*			
0	NO SYMPTOMS	5.	13-24 MOS.
1.	LESS THAN 1 MONTH	6.	25-36 MOS.
2.	1-3 MOS.	7.	MORE THAN 36 MOS.
3.	4-6 MOS.	9	DURATION UNKNOWN
4.	7-12 MOS.		

TREATMENT AND DIAGNOSTIC STATUS PRIOR TO STUDY TREATMENT

WAS PREVIOUS TREATMENT GIVEN? *(Circle one)*	
0.	NO PREVIOUS TREATMENT
1.	NOT KNOWN IF PREVIOUS TREATMENT GIVEN
2.	PREVIOUS TREATMENT GIVEN, TYPE UNKNOWN
3.	PREVIOUS TREATMENT GIVEN, TYPE KNOWN

DIAGNOSIS AT TIME OF EARLIEST ANTI-SYPHILITIC TREATMENT *(Circle one)*			
1.	PRIMARY	6.	CONGENITAL-SPINAL FLUID NOT TESTED
2.	SECONDARY	7.	CONGENITAL-SPINAL FLUID NEGATIVE
3.	SEROPOSITIVE-SPINAL FLUID NOT TESTED	8.	CONGENITAL-SPINAL FLUID POSITIVE
4.	LATENT-BLOOD POSITIVE SPINAL FLUID NEGATIVE	9.	DIAGNOSIS UNKNOWN
5.	NEUROSYPHILIS		

Figure 1A

PREVIOUS ANTISYPHILITIC TREATMENT *(Type and amount when known - multiple choice possible)*

0. NO PREVIOUS TREATMENT
(Adequate routine treatment consists of minimum of 20 injections arsenical and 20 injections heavy metal)

1. "ADEQUATE" ARSENIC AND HEAVY METAL FOR PRIMARY OR SECONDARY SYPHILIS

2. "INADEQUATE" ARSENIC AND HEAVY METAL FOR PRIMARY OR SECONDARY SYPHILIS

3. "ADEQUATE" ARSENIC AND HEAVY METAL AFTER SECONDARY STAGE
APPROX. DATE BEGUN _____ APPROX. DATE COMPLETED _____

4. "INADEQUATE" ARSENIC AND HEAVY METAL AFTER SECONDARY STAGE
APPROX. DATE BEGUN _____ APPROX. DATE COMPLETED _____

5. PENICILLIN

DATE BEGUN	DATE COMPLETED	TYPE	AMOUNT (Mil)	STAGE OF INFECTION AT TIME OF TREATMENT

6. FEVER THERAPY

TYPE	DATE BEGUN	NO. PAROXYSMS OR HOURS (Specify which) (oral 103° rectal 104°)	STAGE OF INFECTION AT TIME OF TREATMENT

9. NOT KNOWN WHETHER PREVIOUS TREATMENT GIVEN; OR IF PREVIOUS TREATMENT GIVEN, TYPE UNKNOWN

REASON FOR STUDY TREATMENT IF PREVIOUSLY TREATED *(Multiple choice possible)*

0. NOT PREVIOUSLY TREATED
1. ELEVATED CELL COUNT DESPITE PREVIOUS TREATMENT
2. ELEVATED PROTEIN DESPITE PREVIOUS TREATMENT
3. POSITIVE CSF WASSERMANN DESPITE PREVIOUS TREATMENT
4. ABNORMAL COLLOIDAL CURVE DESPITE PREVIOUS TREATMENT
5. LACK OF CLINICAL IMPROVEMENT DESPITE PREVIOUS TREATMENT
6. INSUFFICIENT CLINICAL IMPROVEMENT DESPITE PREVIOUS TREATMENT, TO SEE IF PENICILLIN WOULD OFFER POSSIBILITY OF FURTHER IMPROVEMENT
7. CLINICAL PROGRESSION DESPITE PREVIOUS TREATMENT
8. CLINICAL AND LAB STATUS SATISFACTORY BUT PREVIOUS TREATMENT CONSIDERED INADEQUATE
9. FOR NEUROSYPHILIS, REASON DUBIOUS OR UNKNOWN, OR OTHER REASON *(Specify)* _____

WORK STATUS

USUAL OCCUPATION *(Circle one)*

0.	PROFESSIONAL	5.	FARM LABORER
1.	CLERICAL, SALES	6.	STUDENT
2.	SKILLED	7.	MILITARY
3.	UNSKILLED	8.	NO USEFUL WORK
4.	DOMESTIC *(Waitress, housewife, chef, etc.)*	9.	OCCUPATION UNKNOWN

DURATION OF CHANGE IN WORK STATUS BEFORE STUDY TREATMENT *(Circle one)*

0.	NO CHANGE	5.	13-24
1.	LESS THAN ONE MONTH	6.	25-36
2.	1-3 MOS.	7.	MORE THAN 36 MOS.
3.	4-6	9.	DURATION UNKNOWN
4.	7-12		

WORK STATUS AT TIME STUDY TREATMENT STARTED *(Circle one)*

0. NEVER DID USEFUL WORK
1. ABLE TO WORK AT USUAL OCCUPATION
2. ABLE TO WORK AT SIMPLER OCCUPATION
3. UNABLE TO WORK BUT NOT IN MENTAL INSTITUTION
4. IN MENTAL INSTITUTION, ABLE TO WORK THERE
5. IN MENTAL INSTITUTION, UNABLE TO WORK THERE
6. IN MENTAL INSTITUTION, FURTHER STATUS UNKNOWN
9. WORK STATUS UNKNOWN

REASON FOR CHANGE IN WORK STATUS BEFORE STUDY TREATMENT *(Circle one)*

0.	NO CHANGE	3.	OTHER REASON
1.	PARETIC CHANGES	9.	REASON UNKNOWN
2.	NON-PARETIC NEUROSYPHILIS CHANGES		

Figure 1B

SEROLOGIC EXAMINATION

BLOOD SEROLOGIC TESTS *(Latest pretreatment reported in dilutions when possible)*

DATE	TECHNIC	TITER

SPINAL FLUID

All available pretreatment: In a positive test give the smallest amount of fluid giving a positive result (Indicate degree of positivity), e.g.: 4 plus with 0.1 cc. or in a negative, the largest amount of fluid giving a negative result, e.g. negative with 1.0 cc. If more convenient, record actual results of spinal fluid Wass. or Floc. test by dilution tubes, e.g. Kolmer 4&33.

DATE	SPINAL FLUID WASS. OR FLOC. TEST		CELL COUNT	PROTEIN		COLLOIDAL TEST	CHECK IF BLOODY TAP
	TECHNIC	RESULT	RESULT	TECHNIC	RESULT		

By your own clinic standards, do you consider the latest pretreatment:		NORMAL	ABNORMAL
	CELL COUNT		
	PROTEIN		

PENICILLIN TREATMENT FOR NEUROSYPHILIS *(Study treatment)*

DATE BEGUN	DATE COMPLETED COURSE	TYPE *(Multiple choice possible)*	TOTAL UNITS ADMINISTERED
		☐ AQUEOUS ☐ POB ☐ PROCAINE ☐ UNKNOWN	

FEVER TREATMENT FOR NEUROSYPHILIS *(Study treatment)*

0. NO FEVER TREATMENT GIVEN

TYPE	DATE BEGUN	DATE COMPLETED	NO. OF PAROXYSMS *(Oral 103°, rectal 104°)*	NO. OF HOURS *(Oral 103°, rectal 104°)*
MALARIA				
ARTIFICIAL FEVER				
TYPHOID				

HERXHEIMER REACTION DURING FIRST STUDY TREATMENT

(Multiple choice possible)

0. UNDETERMINED	6. DEVELOPMENT (OR) EXACERBATION OF PSYCHOSIS
1. NONE	7. DEVELOPMENT FOCAL VASCULAR ACCIDENT
2. FEVER ONLY	8. DEVELOPMENT RAPID VISUAL FAILURE
3. CLINICAL ONLY	9. DEATH DURING STUDY TREATMENT THOUGHT TO BE HERXHEIMER EFFECT
4. FEVER AND CLINICAL	10. OTHER *(Specify)* _____
5. DEVELOPMENT (OR) ☐ EXACERBATION OF CONVULSIONS	

TIME RELATIONSHIPS

INTERVAL IN HOURS FROM INITIATION OF TREATMENT TO PEAK OF FEVER *(If none, indicate)*

INTERVAL IN HOURS FROM INITIATION OF TREATMENT TO CLINICAL MANIFESTATIONS *(If none, so indicate)*

MAXIMUM ORAL TEMPERATURE *(Fahrenheit)*

DURATION OF FEVER *(Hours)*

DURATION OF CLINICAL MANIFESTATIONS *(Days)*

Figure 1C

THIS PART OF FORM TO BE FILLED IN FOR PARETICS AND TABOPARETICS ONLY

These signs or symptoms are considered important in the diagnosis of paresis. After each one, circle appropriate word which describes the patient's condition.

PSYCHOTIC ON SIMPLE OBSERVATION	NO	YES	ND	(No data or not done)
LOGICAL SEQUENCE TO CONVERSATION	YES	NO	ND	
NEATLY DRESSED	YES	NO	ND	
UNDULY DEPRESSED OR EUPHORIC	NO	YES	ND	
DELUSIONS OR HALLUCINATIONS	NO	YES	ND	
ORIENTED FOR TIME	YES	NO	ND	
ORIENTED FOR PLACE	YES	NO	ND	
ORIENTED FOR PERSON	YES	NO	ND	
RETENTION *(Immediate)* NO. DIGITS FORWARD _____ NO. DIGITS BACKWARD _____			ND	
RETENTION *(Delayed)*	NORMAL	IMPAIRED	ND	
REMOTE MEMORY	NORMAL	IMPAIRED	ND	
RECENT MEMORY	NORMAL	IMPAIRED	ND	
INFORMATION *(For educational level)*	NORMAL	IMPAIRED	ND	
CALCULATION *(For educational level)*	NORMAL	IMPAIRED	ND	
JUDGMENT *(Absurdity tests)*	NORMAL	IMPAIRED	ND	
SPEECH *(Test phrases)*	NORMAL	IMPAIRED	ND	
HANDWRITING	NORMAL	IMPAIRED	ND	
INSIGHT	NORMAL	IMPAIRED	ND	
TREMORS	ABSENT	PRESENT	ND	
CONVULSIONS	ABSENT	PRESENT	ND	
INCONTINENT	NO	YES	ND	
ABLE TO DRESS SELF, ETC.	YES	NO	ND	
EDUCATIONAL LEVEL: NO. SCHOOL YEARS COMPLETED _____				
IS PATIENT CHRONIC ALCOHOLIC?	NO	YES	ND	
IS IT THOUGHT THAT A SENILE ELEMENT IS PRESENT?	NO	YES	ND	

THIS PART OF FORM TO BE FILLED IN FOR PRIMARY OPTIC ATROPHY ONLY

	O.D.				O.S.			
OPTIC DISC COLOR	NORMAL	PALE		ND	NORMAL	PALE		ND
VISION	SNELLEN _____ *(Specify corrected, uncorrected or unknown)*			ND	_____			ND
SCOTOMATA	PRESENT	ABSENT		ND	PRESENT	ABSENT		ND
PERIPHERAL FIELDS	NORMAL	CONCENTRIC CONSTRICTION	SECTOR DEFECT	ND	NORMAL	CONCENTRIC CONSTRICTION	SECTOR DEFECT	ND

ABSTRACTER'S INITIALS _____

Figure 1D

PHS-1630-2
REV. 8-52
FEDERAL SECURITY AGENCY
PUBLIC HEALTH SERVICE

POSTTREATMENT OBSERVATION REPORT
Cooperative Neurosyphilis Study

BUDGET BUREAU NO. 68-R104.1
APPROVAL EXPIRES 8-29-54

PATIENT'S NAME (Last)	(First)	MOS. AFTER STUDY TREATMENT STARTED
CLINIC	PATIENT NO.	DATE PENICILLIN TREATMENT STARTED

FILL IN THIS SECTION FOR PATIENTS NOT AVAILABLE FOR EXAMINATION

DATE DUE FOR EXAMINATION

PATIENT NOT EXAMINED (Circle one)

1. ALIVE, NO FURTHER INFORMATION
2. ALIVE, WORKING, NO FURTHER INFORMATION
3. ALIVE, NOT WORKING, NO FURTHER INFORMATION
4. ALIVE, INSTITUTIONALIZED, NO FURTHER INFORMATION
5. ALIVE, NOT INSTITUTIONALIZED, NO FURTHER INFORMATION
6. DEAD: DATE OF DEATH _____
9. STATUS UNKNOWN

CAUSE OF DEATH (Circle one)

1. CARDIOVASCULAR SYPHILIS
2. NEUROSYPHILIS
3. MALARIA OR OTHER FEVER TREATMENT
4. HERXHEIMER DUE TO PENICILLIN
5. ANY OTHER CAUSE (Specify) _____
9. CAUSE UNKNOWN

SOURCE OF INFORMATION CONCERNING DEATH

WAS POST MORTEM PERFORMED? ☐ YES ☐ NO (If yes, please submit a summary of pertinent post mortem findings)

FILL IN THE REMAINDER OF THIS FORM FOR PATIENTS EXAMINED

BLOOD SEROLOGIC TEST (This observation)

DATE
TECHNIC
TITER
LABORATORY

SPINAL FLUID (This observation)

DATE — CHECK, IF BLOODY TAP ☐

SPINAL FLUID WASS. OR FLOC. TEST:
TECHNIC
RESULT

PROTEIN: TECHNIC
RESULT

CELL COUNT — COLLOIDAL TEST

WEIGHT IN KGS. AT TIME OF THIS OBSERVATION (Circle one)

1. UNDER 40 KGS.
2. 40-49
3. 50-59
4. 60-69
5. 70-79
6. 80-89
7. 90-99
8. 100 KGS OR OVER
9. WEIGHT UNKNOWN

BY YOUR OWN CLINIC STANDARDS, DO YOU CONSIDER:

	NORMAL	ABNORMAL
CELL COUNT		
PROTEIN		

(In evaluation of posttreatment status of taboparesis, base judgment only on paretic component)

CLINICAL STATUS THIS OBSERVATION IN RELATION TO PRE-STUDY TREATMENT STATUS

ASYMPTOMATIC

1. NO PROGRESSION
2. PROGRESSION
   a. MINOR NEUROLOGIC
   b. DEVELOPMENT TABES
   c. DEVELOPMENT PARESIS
   d. DEVELOPMENT POA
   e. OTHER (Specify) _____

PARESIS

1. REMISSION
2. SIGNIFICANT IMPROVEMENT
3. UNCHANGED
4. PROGRESSION
   a. MENTAL
   b. PHYSICAL
   c. MENTAL & PHYSICAL

PRIMARY OPTIC ATROPHY

1. REMISSION
2. SIGNIFICANT IMPROVEMENT
3. UNCHANGED
4. PROGRESSION

IS PROGRESSION BELIEVED TO BE HERXHEIMER EFFECT? ☐ YES ☐ NO

LATEST WORK STATUS (Circle one)

0. NEVER DID USEFUL WORK
1. ABLE TO WORK AT USUAL OCCUPATION
2. ABLE TO WORK AT SIMPLER OCCUPATION
3. UNABLE TO WORK BUT NOT IN INSTITUTION
4. IN MENTAL INSTITUTION, ABLE TO WORK THERE
5. IN MENTAL INSTITUTION, UNABLE TO WORK THERE
6. IN MENTAL INSTITUTION, WORK STATUS UNKNOWN
9. WORK STATUS UNKNOWN

REASON FOR CHANGE IN WORK STATUS SINCE STUDY TREATMENT (Circle one)

0. NO CHANGE
1. IMPROVEMENT OF NEUROSYPHILIS
2. PROGRESSION OF NEUROSYPHILIS
3. OTHER REASON
9. REASON UNKNOWN

Figure 1E

IF PATIENT HAS BEEN RETREATED SINCE LAST TREATMENT RECORDED ON MEDICAL ABSTRACT OR POST-TREATMENT OBSERVATION, FILL OUT THE FOLLOWING:

DATE OF RETREATMENT

REASON FOR RETREATMENT *(Multiple choice possible)*

0. OTHER THAN NEUROSYPHILIS	5. LACK OF CLINICAL IMPROVEMENT DESPITE PREVIOUS TREATMENT
1. ELEVATED CELL COUNT DESPITE PREVIOUS TREATMENT	6. INSUFFICIENT CLINICAL IMPROVEMENT DESPITE PREVIOUS TREATMENT, TO SEE IF PENICILLIN WOULD OFFER POSSIBILITY OF FURTHER IMPROVEMENT
2. ELEVATED PROTEIN DESPITE PREVIOUS TREATMENT	7. CLINICAL PROGRESSION DESPITE PREVIOUS TREATMENT
3. POSITIVE CSF WASSERMANN DESPITE PREVIOUS TREATMENT	8. CLINICAL AND LAB STATUS SATISFACTORY BUT PREVIOUS TREATMENT CONSIDERED INADEQUATE
4. ABNORMAL COLLOIDAL GURVE DESPITE PREVIOUS TREATMENT	9. FOR NEUROSYPHILIS: REASON DUBIOUS OR UNKNOWN, OR OTHER REASON *(Specify)*

TYPE OF RETREATMENT *(Multiple choice possible)*

1. PENICILLIN	2. FEVER	
TYPE	TYPE	
TOTAL UNITS *(Mil)*	NO. PAROXYSMS *(Oral 103°, rectal 104°)*	NO. HOURS *(Oral 103°, rectal 104°)*
3. OTHER *(Specify type and amount)*	9. UNKNOWN TYPE OF RETREATMENT	

THIS PART OF FORM TO BE USED FOR PARETICS AND TABOPARETICS ONLY

PARETIC SYMPTOMS			*(No data or not done)*
PSYCHOTIC ON SIMPLE OBSERVATION	NO	YES	ND
LOGICAL SEQUENCE TO CONVERSATION	YES	NO	ND
NEATLY DRESSED	YES	NO	ND
UNDULY DEPRESSED OR EUPHORIC	NO	YES	ND
DELUSIONS OR HALLUCINATIONS	NO	YES	ND
ORIENTED FOR TIME	YES	NO	ND
ORIENTED FOR PLACE	YES	NO	ND
ORIENTED FOR PERSON	YES	NO	ND
RETENTION *(Immediate)* NO. DIGITS FORWARD _____ NO. DIGITS BACKWARD _____			ND
RETENTION *(Delayed)*	NORMAL	IMPAIRED	ND
REMOTE MEMORY	NORMAL	IMPAIRED	ND
RECENT MEMORY	NORMAL	IMPAIRED	ND
INFORMATION *(For educational level)*	NORMAL	IMPAIRED	ND
CALCULATION *(For educational level)*	NORMAL	IMPAIRED	ND
JUDGMENT *(Absurdity tests)*	NORMAL	IMPAIRED	ND
SPEECH *(Test phrases)*	NORMAL	IMPAIRED	ND
HANDWRITING	NORMAL	IMPAIRED	ND
INSIGHT	NORMAL	IMPAIRED	ND
TREMORS	ABSENT	PRESENT	ND
CONVULSIONS	ABSENT	PRESENT	ND
INCONTINENT	NO	YES	ND
ABLE TO DRESS SELF, ETC.	YES	NO	ND

NO. OF YEARS ADDITIONAL SCHOOLING SINCE STUDY TREATMENT

PATIENT'S ALCOHOLIC STATUS AT THIS OBSERVATION: ☐ SAME ☐ ND *(If changed, describe)* _____

IS IT THOUGHT THAT A SENILE ELEMENT IS PRESENT? ☐ NO ☐ YES ☐ ND

THIS PART OF FORM TO BE USED FOR PRIMARY OPTIC ATROPHY ONLY

	O.D.				O.S.			
OPTIC DISC COLOR	NORMAL	PALE		ND	NORMAL	PALE		ND
VISION	SNELLEN _____ *(Specify corrected, uncorrected or unknown)*			ND	_____			ND
SCOTOMATA	PRESENT	ABSENT		ND	PRESENT	ABSENT		ND
PERIPHERAL FIELDS	NORMAL	CONCENTRIC CONSTRICTION	SECTOR DEFECT	ND	NORMAL	CONCENTRIC CONSTRICTION	SECTOR DEFECT	ND

Figure 1F

The fixed point of reference with respect to time was the so-called "study treatment" date. This was the treatment episode which placed the patient in the study group. For some patients this was the first treatment given for neurosyphilis; for others it represented penicillin given after previous chemotherapy or penicillin therapy which, in the consideration of the clinician, had not been sufficient, so that further treatment was thought necessary. Subsequent to "study treatment" numerous patients were again given penicillin, sometimes because it was felt that the process was progressing or that biologic cure had not been attained. At other times additional penicillin was given in accordance with predetermined treatment schedules, or, occasionally, to allow studying the possible effect of larger doses on spinal fluid reversal. In some cases, penicillin was given as treatment for intercurrent, unrelated illness. Administration of penicillin subsequent to "study treatment" was considered as an incident in follow-up and did not eliminate the patient from the study group.

It was considered advisable to observe the patient 3, 6, and 12 months after "study treatment," and yearly thereafter. The status of the patient described at a time nearest the desired observation interval was accepted as representative of the condition of the patient at that time interval. If a patient observation took place at a stated interval following omission of a scheduled observation, interpolations were made, whenever possible, so as to make some data available for the period during which the patient was not observed.

In evaluating a new modality of therapy, a comparison should ideally be made between control groups of similar, untreated patients and similar patients treated by other methods commonly in use. However, at the present time there is no valid need or justification for an untreated, control group. The course of paresis prior to fever therapy was so invariably unfavorable that death was the common outcome and spontaneous "cure" or improvement was notable for its rarity. The experience is best summarized by quotations taken from several authors with large experience in this field. Stokes[2] characterizes paresis as follows:

The course of paretic neurosyphilis varies remarkably in different patients. An acute fulminating or galloping form occurs, with an encephalitic picture and fever or with rapidly successive seizures or shocks, each leaving the patient more deteriorated than the preceding, and terminating often in the fatal convulsive state. . . . The excited type with flight ideas, delusions, extreme irritability and outbursts of maniacal violence is contrasted with the silent, depressed, and suicidally inclined patient, and with the slow deteriorative type which gradually declines into silliness, dementia, and amentia. The mental characteristics which constitute the average conception of paretic neurosyphilis belong simply to a median type whose euphoria, fabrication, and grandiose delusions during a physical decline unaccompanied by any consciousness of course or termination, is the medical apotheosis of an easy death. . . .

Moore[3] describes the outcome of untreated paresis.

Without treatment, complete remissions infrequently occur in paresis (3-5 percent). When they do occur, they are almost always of short duration, a few months only. Temporary partial improvement also occurs in a few patients (5-15 percent), also of short duration. In the large majority, there is steady downhill progression with death following the onset of symptoms in an average of 2 years. An exceptional patient may live 5 years or longer.

A few selected reports from the vast literature on this subject also have been tabulated showing the experience in the premalarial therapy era (Table 1).

It is perhaps well to quote Dattner[4] to provide an adequate summary of the historic control against which our experience must be judged.

No more than two decades ago it [paresis] was considered incurable. In a series of 2,500 paretic patients, Krafft-Ebing did not find a single cured case, nor did Junius and Arndt in 900 patients. Hoche, in his monograph on general paresis, writes that in twenty years of clinical experience he never saw a cured paretic. This belief became so firmly established that at the International Medical Congress in Paris in 1922 (in the discussion of a paper read by Bruce, of Edinburgh) it was stated that there is no therapy for paretics. The same statement was made in the neuropsychiatric section of the British Medical Society in Glasgow in the same year, when Robertson was its chairman.

TABLE 1.—*Summary of Selected References on the Outcome of Untreated Paresis*

Reference	Date and Place of Study	No. of Patients Observed	Outcome of Untreated Paresis
Lewis, Hubbard, and Dyar [7]	1886-1923 St. Elizabeths Hospital, Washington, D. C.	1,558	Death within 3 yr. after hospitalization, 67.5%
Woodman [8]	1907-1917	111	Average duration of life: 26 mo. after admission
	1917-1925 Middletown State Hospital	86	15.8 mo. after admission
Briner [9]	1903-1929 Psychiatric Clinic, Zurich	470	Lived less than 3 yr., 70%
Derby [10]	1917-1921 Brooklyn State Hospital	239	Average duration of life, 1.5 yr. after admission
Cheney [11]	1920 New York State Hospital	Patients admitted during 1920	Death within 4 yr., 82.1%
Dattner [4]	1920-1923 London County Hospitals	227	Lived less than 3 yr. after admission, 62.1%

When the first successes of malaria therapy became known, doubts were expressed as to whether the treated patients really were paretics and not patients with meningovascular syphilis. Not until Robertson was assured by von Pirquet of Wagner-Jauregg's trustworthiness did he himself introduce the malaria experiment in Scotland.

Against this background of untreated general paresis the discussion of the experience of treatment with penicillin alone or penicillin with fever follows.

The Material

No untreated control group is available, but the end-point in untreated paresis, as evidenced by the previous discussion of the literature prior to the introduction of malaria therapy in 1917, is death, usually within a period of four years from detection.

Composition and Characteristics of Study Group.—An outline summary of the composition and characteristics of the 1,086 patients at time of study treatment, together with brief comments, follows.

Race and Sex

	No.	Per Cent
White male	580	53.4
White female	178	16.4
Negro male	226	20.8
Negro female	99	9.1
Other	3	0.3

Comment. Paresis is seen approximately three times as frequently in males as in females and over twice as frequently in whites as in Negroes.

Age

Years	No.	Per Cent
1-29	69	6.3
30-39	255	23.5
40-49	444	40.9
50-59	223	20.5
60 and over	77	7.1
Unknown	18	1.7

Comment. Paresis strikes most frequently during life's most productive years (85% aged 30-59 years).

Previous Treatment

Treatment	No.	Per Cent
None	327	30.1
Metals	371	34.2
Penicillin	56	5.2
Fever	112	10.3
Unknown	220	20.2

Comment. Information as to previous treatment was unavailable in a large number of cases. Of those patients for whom such information was available, almost 40% had been entirely untreated, and very few patients had received penicillin. Consideration of the stage of infection when first treatment was given revealed that only 10% of the patients had received any treatment for early syphilis. In no case had this treatment for early syphilis included penicillin.

Duration of Infection

In paretics this is usually at best a rough estimate, for obvious reasons. In 569

(52.4%) of the present group no estimate as to duration of infection could be made. The estimated duration in the remainder ranged from 2 to 30 years or more, with the majority falling in the period of 10 to 24 years.

Duration of Paretic Symptoms

Months	No.	Per Cent
0-3	173	15.9
4-6	117	10.8
7-12	194	17.9
13-24	142	13.1
25-36	71	6.5
37+	166	15.3
Unknown	223	20.5

Comment. In paretics the great difficulty of obtaining a reliable history as to duration of symptoms is well known. In 20.5% of the present group duration of symptoms was unknown. Ideally, paresis should be promptly diagnosed and as promptly treated. The present group represents a far different situation, with only 15.9% of the patients entering the study with symptoms of three months' duration or less. The results of treatment herein reported may thus be considered minimal.

Spinal Fluid Data

Cell Count	No.	Per Cent
0-4	247	22.7
5-10	178	16.4
11-30	290	26.7
31 or more	304	28.0
Unknown	67	6.2
Protein, Mg. %	No.	Per Cent
Less than 40	184	16.9
40-50	174	16.0
51-98	423	39.0
99 or more	232	21.4
Unknown	73	6.7
Wassermann Test	No.	Per Cent
Total	953	100.0
Positive	938	98.4
Doubtful	3	0.3
Negative	5	0.5
Bloody tap	7	0.8
Kahn Test	No.	Per Cent
Total	133	100.0
Positive	124	93.2
Doubtful	1	0.8
Negative	8	6.0

Titered Wassermann Test

Least amount of spinal fluid giving positive test

	No.	Per Cent
Total titered	834	100.0
0.1 cc. or less	580	69.5
0.2 cc.	189	22.7
0.4 cc.	30	3.6
0.5-0.6 cc.	20	2.4
0.8 cc.	8	1.0
0.8-1.0 cc., doubtful	2	0.2
0.8-1.0 cc., negative	5	0.6

Comment. The relative frequency of an inactive spinal fluid (cells 0-4; protein less than 40 mg. %) preceding study treatment is best explained by previous treatment. It is well known that arsenic and heavy metals will frequently temporarily depress cell count and protein level, although the paretic process is not fundamentally altered. In untreated paresis the spinal fluid cell count is in most cases elevated. In the present group, approximately 85% of the previously untreated cases had a pretreatment cell count of 5 or more per cubic millimeter.

The spinal fluid Wassermann test was almost always positive, and, when titered, usually with small amounts of spinal fluid. Not so the blood serologic test, which was negative in no less than 93 (8.6%) of the patients. In untreated paresis, a positive spinal fluid Wassermann test is a *sine qua non* for the diagnosis, but the blood serologic test may be negative. All previously untreated patients in the present group had positive spinal fluid Wassermann test findings either at the time of or just prior to the administration of penicillin. Twenty-six (8.0%) of the 327 previously untreated patients had negative blood serologic tests at the time of study treatment.

The Psychosis

Severity of psychosis	No.	Per Cent
Mild	241	22.2
Moderate	234	21.5
Severe	611	56.3
Type of psychosis		
Simple demented	649	59.8
Manic, expansive	197	18.1
Depressed	63	5.8

Paranoid	69	6.4
Diagnosis on somatic grounds alone	35	3.2
Type unclassified	73	6.7

Comment. The basis for classification as to severity is discussed in detail below. This present group is a relatively severely affected one and a good test group for the evaluation of treatment. The simple demented type of psychosis is more frequent than all others combined. Twenty per cent of these patients also had tabes, but evaluation of the effects of treatment has been based entirely upon paretic symptoms.

Severity of Paretic Psychoses.—In order to provide some basis for prognosis and for valid comparison of other variables, the severity of clinical paretic involvement at time of treatment has been estimated. Classification of cases as mild, moderate, or severe has therefore been made according to the criteria set forth in Table 2.

TABLE 2.—*Classification of General Paresis*

Group 1: Symptoms indicative of *severe* paretic involvement
1. Psychotic on simple observation
2. Delusions
3. Disorientation for time
4. Disorientation for place
5. Disorientation for person
6. Incontinence
7. Untidy dress
8. Illogical sequence to conversation
9. Inability to dress self

Group 2: Symptoms indicative of *less severe* paretic involvement
1. Impaired immediate retention
2. Impaired delayed retention
3. Impaired recent memory
4. Impaired remote memory
5. Impaired capacity for information
6. Impaired capacity for calculation
7. Impaired judgment
8. Impaired insight
9. Impaired speech
10. Impaired handwriting
11. Tremors

Classification on the basis of symptom * groups

Severe: To be classified as having severe paresis, a patient must have had two or more of the symptoms listed in Group 1 at time of study treatment.

Moderate: To be classified as having moderate paresis, a patient must have had only one or none of the symptoms in Group 1, but five or more of the symptoms in Group 2.

Mild: To be classified as having mild paresis, a patient must have had only one or none of the symptoms in Group 1 and less than five of the symptoms in Group 2.

* Convulsions, since they represent a residual of damage, as well as being a symptom specific of general paresis, have been omitted from consideration in the classification. Undue depression and euphoria, representing mood changes, also are omitted because of the difficulty in objective measurement.

Severe paretic involvement was present in 56.3%, moderate involvement in 21.5%, and mild involvement in 22.2% of the 1,086 patients. The fact that the two cooperating psychiatric hospitals contributed 375 of the 611 severe cases strongly supports the validity of the classification.

Study of distribution by age, race, and sex failed to reveal any definite correlation with severity of involvement.

Consideration of the type of psychosis revealed, as expected, that a preponderance of patients with manic-expansive or paranoid psychosis was classified as severely involved and that patients diagnosed as having "questionable paresis" or diagnosed on somatic grounds alone fell preponderantly into the milder categories.

The presence or absence of previous treatment, the type of previous treatment, and the diagnosis at time of earliest antisyphilitic therapy did not seem to influence the severity of involvement. It was difficult to assess the possible importance of duration of syphilitic infection, which was unknown in over one-half the patients. The effect of duration of paretic symptoms was not evident from our data. The large number (20.5%) of patients in whom the duration was unknown and the great difficulty in obtaining a reliable history in this regard were doubtless the chief reasons for lack of correlation between duration of symptoms and severity of involvement.

Sometimes in a study such as this, which runs over a decade (1943-1953), criteria for inclusion of cases change. It is therefore important to note that there was no correlation between severity of paretic involvement and year of study treatment in the present material.

Detailed study failed to reveal any correlation between initial spinal fluid cell count or protein content and severity of clinical paretic involvement.

As shown in Table 3, the classification adopted correlates well with pragmatic clas-

TABLE 3.—*Work Status at Time of Study Treatment, by Degree of Paretic Involvement*

Work Status	Total		Degree of Paretic Involvement					
			Severe		Moderate		Mild	
	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent
Able to work at usual occupation	168	15.5	--	--	55	23.5	113	46.9
Able to work at simpler occupation	54	5.0	18	2.9	23	9.8	13	5.4
Unable to work—not institutionalized	297	27.3	170	27.8	74	31.6	53	22.0
Institutionalized—								
Able to work there	37	3.4	20	3.3	6	2.6	11	4.6
Unable to work there	456	42.0	359	58.7	63	26.9	34	14.1
Status unknown	1	0.1	1	0.2	--	--	--	--
In prison	5	0.4	3	0.5	--	--	2	0.8
Never did useful work	6	0.6	3	0.5	2	0.9	1	0.4
Status unknown	62	5.7	37	6.1	11	4.7	14	5.8
Total	1,086	100.0	611	100.0	234	100.0	241	100.0

sification based upon work status.‡ Only 2.9% of the paretics classified as severe were able to work and were not institutionalized at time of study treatment, as contrasted with 33.3% and 52.3% of those classified as moderate and mild, respectively.

Consideration has been given to extraneous factors which might conceivably influence proper interpretation of severity of paretic psychoses. The patient's intelligence before the development of paresis is certainly a most important factor, and one which, in the present study, it has not been possible to evaluate. The extent of this problem is exemplified by 83 patients (7.7%) who were classified as having simple demented paresis, diagnosis questionable. This reflects the inability of experienced clinicians definitely to differentiate paresis from mental retardation or from psychoses other than paresis, even in the presence of typical spinal fluid findings. It must be recognized that a small proportion of the present group of 1,086 patients, therefore, represents asymptomatic neurosyphilis plus mental retardation, alcoholism, cerebral arteriosclerosis, or other psychoses, rather than paresis. Since these other forms of mental aberration are not influenced by penicillin, their inclusion tends to minimize the results of treatment.

Educational level has not proved to be a formidable barrier to proper classification. Severe involvement was found in 61.3% of the patients with eight years or less of schooling and in 56.5% with more than eight years of schooling. This would indicate that lack of education in the patient has not often misled the clinicians.

Chronic alcoholism was considered to be present in 118 of the 1,086 patients. Sixty-nine per cent of these 118 patients were classified as having severe paresis, as compared with 56.2% of the nonalcoholic patients, a difference best interpreted as additive rather than etiologically significant.

Since only 77 of the 1,086 patients were 60 years or older, a confusing senile element could not have been very frequent. However, the precentage of this age group classified as "severe" did not significantly differ from the percentage of younger age groups similarly classified. A senile element was thought to be present at the time of study treatment in 26 (2.4%) of the 1,086 patients.

Study Treatment

Study treatment, defined as that course of treatment placing the patient in this series and serving as a reference point in time, consisted of aqueous penicillin in 85% of the 1,086 patients, procaine peni-

‡ The reason for decrease in work capacity as compared with usual work capacity at time of study treatment was known in 802 patients. In 776 (97%) of these patients the decrease was due to paretic neurosyphilis and in 26 (3%), to extraneous factors.

TABLE 4.—*Amount of Penicillin Used at Study Treatment*

Amount of Penicillin, Million Units	Patients Treated	
	No.	Per Cent
Less than 0.6	6	0.5
0.6-1.199	3	0.3
1.2-2.399	23	2.1
2.4-4.799	352	32.4
4.8-5.999	77	7.1
6.0-8.999	417	38.4
9.0-9.999	155	14.3
10.0 or more	53	4.9
Total	1,086	100.0

cillin in 12%, and penicillin in oil and wax or mixed types in the remaining 3%. Table 4 shows the distribution with respect to amount of penicillin used. Ninety-seven per cent of the patients received more than 2,400,000 units, and 58% received more than 6,000,000 units. There was a definite tendency to treat clinically severe paretics with a larger dosage. Thus, 63% of severe paretics and only 50% of the moderate and mild paretics received 6,000,000 units or more.

As shown in Table 5, there was a similar tendency to add fever therapy to penicillin significantly more frequently in the severe than in the moderate cases and in the moderate more frequently than in the mild cases of paresis. A total of 457 patients were treated with fever plus penicillin and 629 patients were treated with penicillin alone.

Fever treatment consisted of induced malaria in 86%, artificial fever in 8%, and various combinations of the two with or without typhoid vaccine therapy in the remaining 6%, of the 457 patients.

The trend in recent years has been toward the utilization of penicillin alone. Of 808 patients treated during 1943-1947, 49% received fever therapy, as compared with only 22% of 278 patients treated during 1948-1953. No patient received fever subsequent to 1950.

Table 6 shows the observation periods in years after study treatment.

The fact that 91.5% of 1,086 paretics were followed one year or more, 78.5% three years or more, 59.6% five years or more, and 33.7% seven years or more represents a remarkable achievement among eight cooperating clinics located in various sections of the country. It lends validity to the conclusions of the present study—an effort which, in view of the diminishing incidence of syphilis, it may never again be possible to duplicate in the United States.

The Herxheimer Reaction

A clinical Herxheimer reaction is defined, for purposes of the present study, as an

TABLE 5.—*Fever Therapy by Degree of Paretic Involvement*

Fever Therapy	Total		Severe Paresis		Moderate Paresis		Mild Paresis	
	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent
Fever administered	457	100.0	281	61.5	93	20.3	83	18.2
No fever administered	629	100.0	330	52.5	141	22.4	158	25.1
Total	1,086	100.0	611	56.3	234	21.5	241	22.2

TABLE 6.—*Observation Period After Study Treatment*

Post-Treatment Observation Period	Study Patients	
	No.	Per Cent
Not seen after treatment	7	0.7
3 mo.	1,079	99.3
6 mo.	1,031	94.9
1 yr.	983	91.5
2 yr.	936	86.2
3 yr.	852	78.5
4 yr.	757	69.7
5 yr.	647	59.6
6 yr.	499	46.0
7 yr.	365	33.7
8 yr.	203	18.8
9 yr.	95	8.8
10 yr.	16	1.5

exacerbation of neurosyphilis symptoms occurring within a few days after the initiation of treatment. A febrile Herxheimer reaction is manifested by fever alone. The incidence of Herxheimer reactions was unrelated to the clinical severity of the paretic psychosis. The relation of the incidence of the Herxheimer reaction to the activity of the syphilitic process in the central nervous system has previously been pointed out in a study of the Johns Hopkins material [5] and is confirmed in the present study. Among 425 patients whose pretreatment spinal fluids contained less than 11 cells per cubic millimeter, febrile Herxheimer reactions occurred in 27 (6.4%) and clinical Herxheimer reactions in 7 (1.6%). Among 594 patients whose pretreatment spinal fluids contained 11 cells or more, febrile Herxheimer reactions occurred in 59 (9.9%) and clinical Herxheimer reactions in 31 (5.2%). No such clear-cut relationship of Herxheimer reactions to spinal fluid protein level was demonstrable.

Febrile Herxheimer reactions were recorded in 94 (14.9%) of 629 patients treated with penicillin alone. This represents the minimum incidence, since temperatures were not recorded in many cases. The incidence of febrile Herxheimer reactions could not be estimated, for obvious reasons, among 457 patients treated with fever therapy plus penicillin. Clinical Herxheimer reactions occurred with strikingly greater frequency among the 629 patients treated with penicillin alone (36, or 5.8%) than among the 457 patients treated with penicillin plus fever (8, or 1.8%), thus confirming a previous clinical observation of Moore.[6]

Among the 44 clinical Herxheimer reactions, exacerbation of psychosis and development of convulsive seizures were the major problems, occurring in 24 and 6 patients, respectively. Either of these situations may constitute a grave, even though usually more or less temporary, clinical emergency, often necessitating immediate hospitalization of ambulatory patients. Adequate pretreatment sedation is recommended, and anticonvulsant therapy is advisable if there is any history of seizures.

There was one death in the present series clearly due to a Herxheimer reaction.

A 45-year-old Negro man was admitted to St. Elizabeths Hospital with simple demented paresis. The symptoms, forgetfulness and crying spells, appeared in July, 1944. Spinal fluid examination on Dec. 19, 1944, showed 31 cells per cubic millimeter, 100 mg. % of protein, Wassermann test 4444, and mastic test 55553333110. On Dec. 20, therapy with an aqueous solution of penicillin was started, with the schedule of 25,000 units every three hours. Following the fourth dose of penicillin, with a total dose of 100,000 units up to that time, the patient developed fever and convulsive seizures and died approximately 14 hours later. Permission to perform an autopsy was refused.

This case and one death due to induced malaria constitute the total treatment mortality (0.18%) in the present group of 1,086 paretic patients.

Results of Treatment

Since the favorable effects of penicillin on the cerebrospinal fluid have been previously well documented,[1,5] current interest centers largely upon the effect of penicillin with or without fever therapy upon the clinical status. In the present study two measurements of clinical outcome have been utilized.

1. *Clinical Status of the Paretic Psychosis at Each Post-Treatment Observation in Relation to Pretreatment Status.*—In this determination the judgment of the clinician was paramount. The possible categorizations were remission or significant improvement, unchanged status, progression, or death. Death was further categorized as to cause—neurosyphilis and other causes.

2. *Work Status at Each Post-Treatment Observation in Relation to Pretreatment Status.*—This is a pragmatic yardstick of evaluation largely independent of the vagaries of individual clinical judgment, but subject to a variety of imponderable, general extraneous influences, such as the business cycle, interest of relatives in helping patients, availability of vocational rehabilitation, and availability of suitable

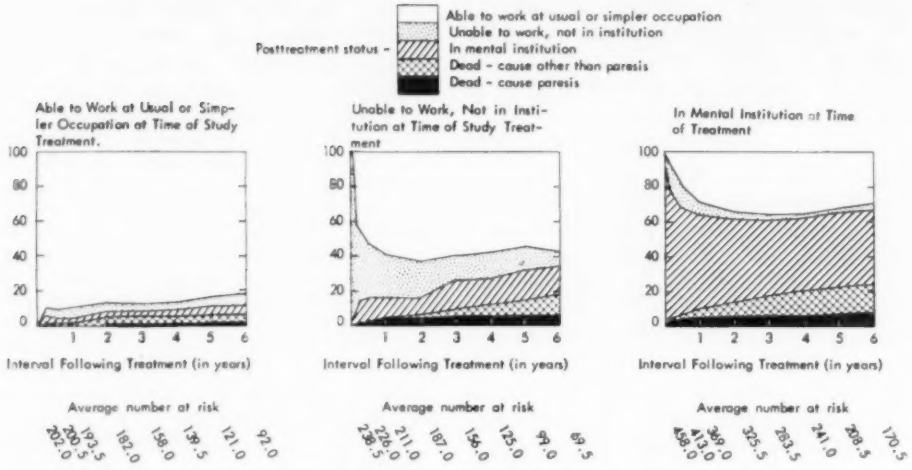

Posttreatment status –
Able to work at usual or simpler occupation
Unable to work, not in institution
In mental institution
Dead – cause other than paresis
Dead – cause paresis
Able to Work at Usual or Simpler Occupation at Time of Study Treatment.
Unable to Work, Not in Institution at Time of Study Treatment
In Mental Institution at Time of Treatment
Interval Following Treatment (in years)
Average number at risk
202.0 200.5 193.5 182.0 158.0 139.5 121.0 92.0
238.5 226.0 211.0 187.0 156.0 125.0 99.0 69.5
458.0 413.0 369.0 325.5 283.5 241.0 208.5 170.5

Fig. 2.—Post-treatment work status, by work status at study treatment.

work. The possible categorizations were ability to work at the usual or simpler occupation, inability to work but not in mental institution, and in mental institution.

By means of a modified life table technique, the study group has been described first as survivors and deaths, with all patients carried through to the latest observation, death, or re-treatment. The survivors then are further categorized in relation to pretreatment status. Results are expressed in graphic form, the actual life tables being omitted.§

Work Status Relationship: Post-treatment work status in relation to work status at time of study treatment is presented in Figure 2. For this evaluation 901 cases were available. Those patients whose inability to work was for other than reasons of paresis were excluded. Also excluded were patients with unknown occupation, consideration being limited to (1) professional, clerical, and sales persons; (2) skilled manual workers; (3) unskilled and farm laborers, and (4) domestic workers. Work status at time of study treatment was remarkably similar for all four occupational groups.

Significant numbers of patients have been followed through the sixth or seventh year of post-treatment observation. At six years' post-treatment observation, 82% of those able to work before treatment continued to be able to work. Of those unable to work but not institutionalized before treatment 56% were rehabilitated for work, while of those institutionalized before treatment 33% were rehabilitated for work. Psychiatric institutionalization was necessary at six years for 4%, 17%, and 42% of these groups, respectively. Death due to neurosyphilis had occurred in 1%, 5%, and 6%, respectively. Figure 2 illustrates two important points: First, one out of three institutionalized paretic patients can be rehabilitated for work; and, second, pretreatment work status is of prognostic import.

Ability to work at four years after treatment was inversely proportional to the length of time decreased work capacity had existed at the time of treatment. If decreased work capacity had existed more than a year prior to treatment, only 31% were able to work 4 years later, as contrasted with 41% of those with decreased work capacity of 7-12 months' duration;

§ The actual life tables are on file in the Office of Statistics, Venereal Disease Branch, Communicable Disease Center, Public Health Service, U. S. Department of Health, Education, and Welfare, Atlanta, Ga.

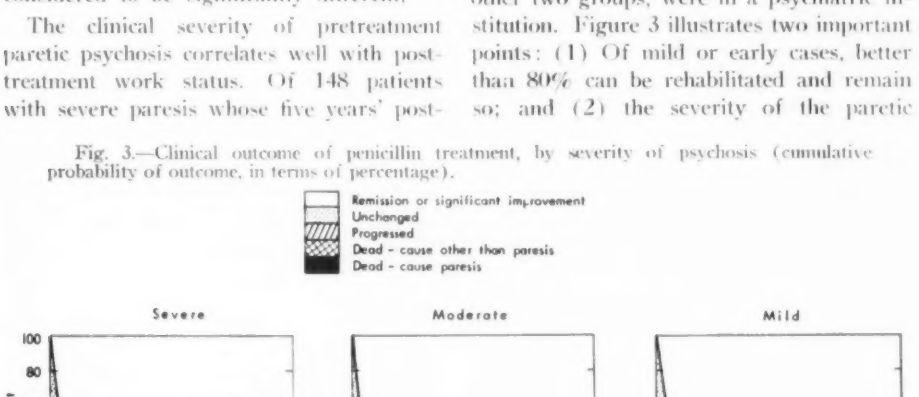
49%, 4-6 months' duration; 57%, 1-3 months' duration; 62%, less than 1 month's duration, and 81%, without decreased work capacity at time of treatment. The percentage of patients in a psychiatric institution four years after treatment was directly proportional to duration of decreased work capacity at time of treatment: 43%, 39%, 21%, 25%, 18%, and 9% for the above groups, respectively. It is evident that not only is absolute work status at time of treatment of prognostic import but perhaps of equal significance is the length of time which has elapsed since the patient has been able to work at his usual occupational level.

Study of outcome according to usual occupation was not feasible, owing to the small number of cases available after subcategorization. Among institutionalized patients there were, however, 118 skilled workers and 215 unskilled or farm laborers, with significant numbers followed through five years of post-treatment observation. At that time 39% of the former and 30% of the latter were able to work, results not considered to be significantly different.

The clinical severity of pretreatment paretic psychosis correlates well with post-treatment work status. Of 148 patients with severe paresis whose five years' post-treatment work status was known, 55 (37%) were able to work, as compared with 50 (82%) of 61 with moderate paresis and 56 (92%) of 61 with mild paresis. The clinicians' evaluation of clinical status at each post-treatment observation in relation to pretreatment status correlated well with work status as recorded at the same observation.

Outcome in Relation to Severity of Psychosis: Figure 3 presents clinical outcome for the group as a whole in relation to severity of paretic psychosis. Significant numbers of patients have been followed through the seventh year of post-treatment observation. At that time the *salvage rate* (expressed as "remission or significant improvement" for severe and moderate cases and as "remission, significant improvement, or unchanged" for the mild cases) was 38.0% for the severe group, 74.0% for the moderate group, and 81.4% for the mild group. Progression and death *due to neurosyphilis* occurred preponderantly in the severe group. At seven years, 35.2% of this group, as compared with 7.3% of the other two groups, were in a psychiatric institution. Figure 3 illustrates two important points: (1) Of mild or early cases, better than 80% can be rehabilitated and remain so; and (2) the severity of the paretic

Fig. 3.—Clinical outcome of penicillin treatment, by severity of psychosis (cumulative probability of outcome, in terms of percentage).



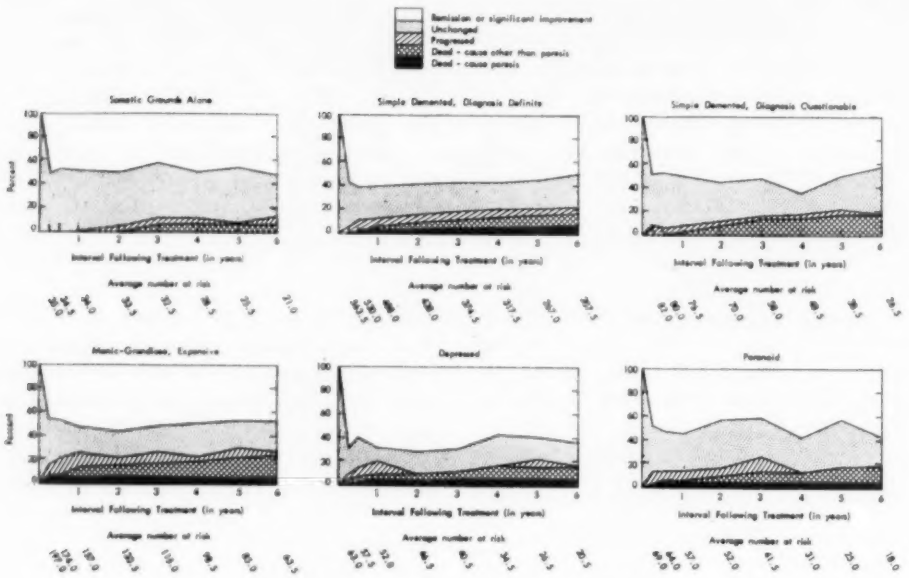


Fig. 4.—Clinical outcome, by type of psychosis.

psychosis at time of treatment is of considerable prognostic import.

Outcome in Relation to Type of Psychosis: Figure 4 presents clinical outcome in relation to type of psychosis rather than severity of psychosis. Only in the "simple demented, diagnosis definite" group and the "manic-grandiose, expansive" group were significant numbers of patients followed six years after treatment. Outcome in these two groups was not markedly at variance. As expected, the small groups of patients diagnosed as paretic on somatic grounds alone and those with only questionable psychosis did well.‖ The outcome in depressed patients seemed to be relatively favorable, also. Even the paranoid group showed a significant rate of improvement, although less than in any other type. Death rates due to neurosyphilis were unrelated to type of psychosis, but deaths did not occur at all in the "somatic only" or "questionable" groups.

At five years after treatment 47.3% of patients with simple demented paresis (diagnosis definite) were able to work, and 30.9% were in a psychiatric institution. In comparison, the "manic-grandiose, expansive" paretic did somewhat less well, with only 26.5% able to work and 40.4% in a psychiatric institution. Work status outcome was much more favorable in the relatively small groups of paretics diagnosed as such on somatic grounds alone or with questionable psychoses. Depressed patients did relatively well, and paranoid patients, least well, although in all these four groups the number followed for five years was too small to allow quotation of actual percentages.

It is clear from the above discussion that type of psychosis is of less importance prognostically than is severity of psychosis, and that patients with so little mental aberration as to fall into the "questionable" or "somatic only" categories have the best prognoses. The importance of early diagnosis and prompt treatment of paresis is thus once again demonstrated.

Outcome in Relation to Spinal Fluid Activity: Figure 5 presents clinical outcome

‖ For these mild cases "unchanged" status constituted a good clinical result.

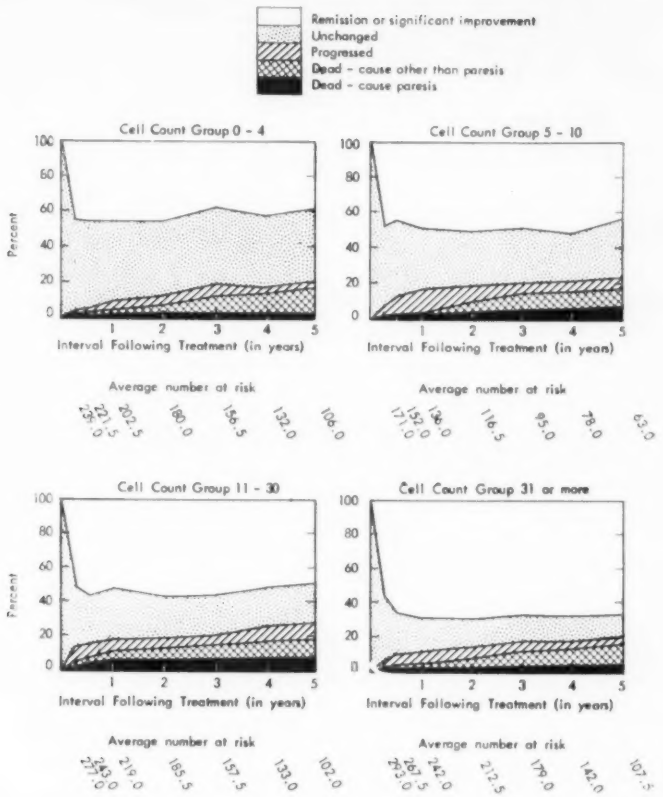

Remission or significant improvement
Unchanged
Progressed
Dead – cause other than paresis
Dead – cause paresis
Cell Count Group 0 – 4
Cell Count Group 5 – 10
Cell Count Group 11 – 30
Cell Count Group 31 or more
Percent
Interval Following Treatment (in years)
Average number at risk
263.5 221.0 202.5 180.0 156.5 132.0 106.0
171.0 152.0 136.0 116.5 95.0 78.0 63.0
257.0 219.0 185.5 157.5 133.0 102.0
263.5 242.0 212.5 179.0 142.0 107.5

Fig. 5. — Clinical outcome, by pretreatment spinal fluid cell count.

in relation to spinal fluid cell count ¶ at the time of study treatment. Significant numbers of patients have been followed through the fifth year of post-treatment observation. At that time remission or improvement occurred in 39.5% of patients with initial cell count of 0-4, in 44.0% with initial cell count of 5-10, in 49.4% with initial cell count of 11-30, and in 64.9% with initial cell count of 31 or more. Apparently, but not truly paradoxically, progression rates were slightly higher in patients with active pretreatment spinal fluid: 3%, 4.9%, 9.5%, and 4.8%, respectively. Deaths due to neurosyphilis more or less paralleled progression rates. Figure 5 illustrates the fact that an elevated pretreatment spinal fluid cell count indicates an active inflammatory process more susceptible of improvement by treatment, but, at the same time, in some cases, leaving behind sufficient brain damage to nullify any real clinical effect. Patients with an inactive fluid, on the other hand, have a relatively static process, less susceptible to improvement by treatment but, at the same time, less likely to result in clinical progression. The correlation is definite enough to be of some prognostic value, but not suffi-

¶ Pretreatment cell count and protein level were found to have a close inverse relationship to duration of symptoms at time of study treatment. Median duration of symptoms was 22.9 months for patients with 0-4 cells, 11.2 months for patients with 5-10 cells, 10.0 months for patients with 11-30 cells, and 9.1 months for patients with 31 cells or more. Median duration of symptoms was 22.1 months for patients with protein of less than 40 mg. %; 11.5 months, with protein of 40-50 mg. %; 10.6 months, with protein of 51-98 mg. %, and 9.2 months, with protein of 99 mg. % or more.

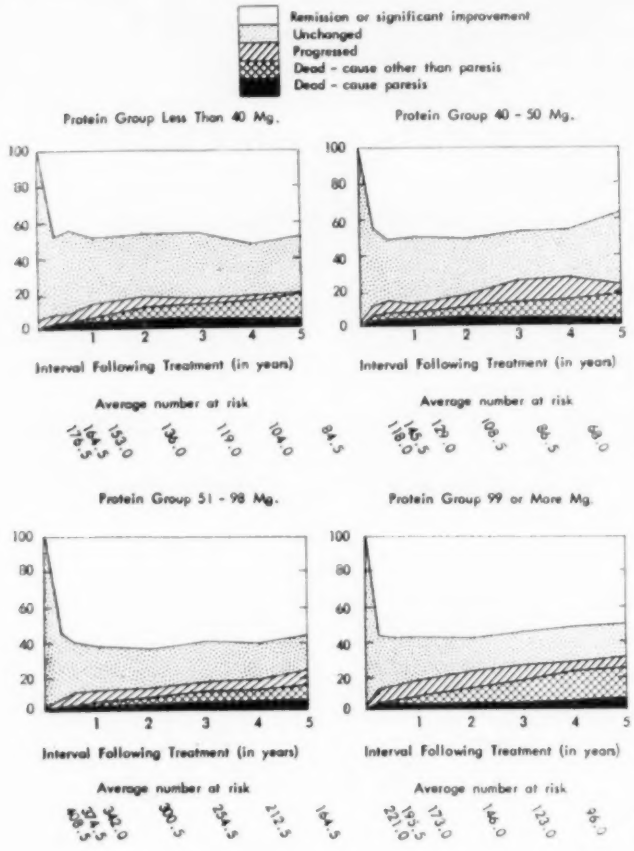

Remission or significant improvement
Unchanged
Progressed
Dead – cause other than paresis
Dead – cause paresis
Protein Group Less Than 40 Mg.
Protein Group 40 – 50 Mg.
Protein Group 51 – 98 Mg.
Protein Group 99 or More Mg.
Interval Following Treatment (in years)
Average number at risk

Fig. 6. — Clinical outcome, by pretreatment protein level.

ciently great to permit withholding adequate treatment from any paretic who has not had adequate treatment previously.

Pretreatment spinal fluid protein level (Fig. 6) showed the same general relationship to clinical outcome as did pretreatment spinal fluid cell count, but the correlation was not as striking. At the fifth year of post-treatment observation, remission or significant improvement had occurred in only 40% of patients whose pretreatment fluids showed normal cell count and protein level, as contrasted with 58.5% of patients with elevated pretreatment cell count and protein level. There was no progression in the former group, but 7.2% in the latter.

Figure 7 presents post-treatment work status in relation to spinal fluid cell count at time of study treatment. Significant numbers of patients have been followed through the sixth year of post-treatment observation. At that time 50.4% of patients with initial cell counts of 31 or more were able to work, as contrasted with 41.7%, 46.5%, and 39.6% for the 0-4, 5-10, and 11-30 cell count groups, respectively. Psychiatric institutionalization was necessary for fewer of the patients with high pretreatment cell counts. Pretreatment spinal fluid protein level showed the same general relationships. At the sixth year of post-treatment observation 41% of the patients whose pretreatment fluids showed normal cell count and protein content were able to work, as contrasted with 44.8% of the patients with elevated pretreatment cell count

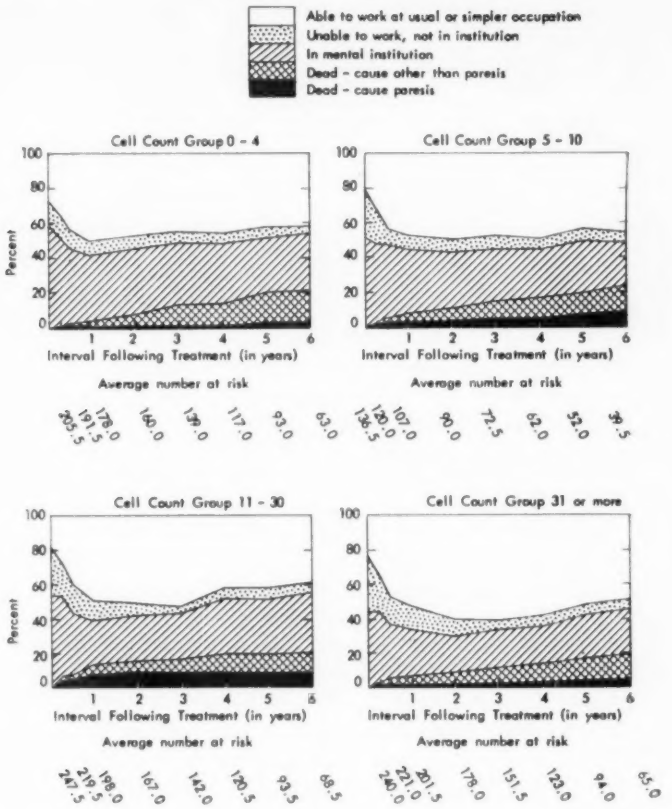

Able to work at usual or simpler occupation
Unable to work, not in institution
In mental institution
Dead – cause other than paresis
Dead – cause paresis
Cell Count Group 0 – 4
Cell Count Group 5 – 10
Cell Count Group 11 – 30
Cell Count Group 31 or more
Percent
Interval Following Treatment (in years)
Average number at risk
205.5 191.5 178.0 160.0 139.0 117.0 93.0 63.0
136.5 120.0 107.0 90.0 72.5 62.0 52.0 39.5
247.5 219.5 198.0 167.0 142.0 120.5 93.5 68.5
240.0 221.0 201.5 178.0 151.5 123.0 94.0 65.0

Fig. 7.—Post-treatment work status, by pre-treatment spinal fluid cell count.

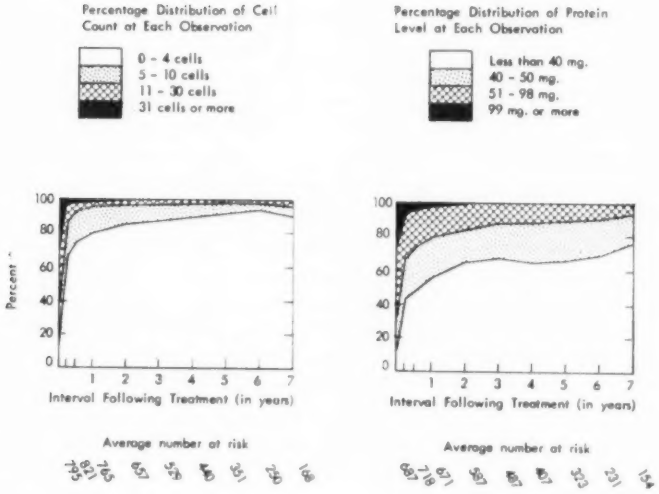

Percentage Distribution of Cell Count at Each Observation
0 – 4 cells
5 – 10 cells
11 – 30 cells
31 cells or more
Percentage Distribution of Protein Level at Each Observation
Less than 40 mg.
40 – 50 mg.
51 – 98 mg.
99 mg. or more
Percent
Interval Following Treatment (in years)
Average number at risk
745 457 328 260 188
719 487 323 231 154

Fig. 8.—Spinal fluid cell count and protein level at each post-treatment observation.

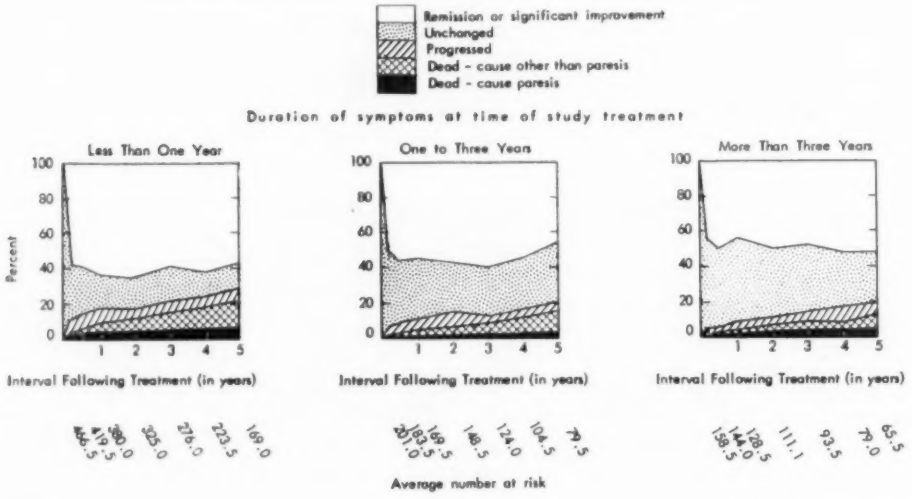
and protein content. Thirty-seven per cent of the former and only 30% of the latter were in a psychiatric institution. The correlations between post-treatment work status and pretreatment spinal fluid activity are less striking than, but confirmatory of, the previously discussed correlations between clinical outcome and pretreatment spinal fluid activity.

Spinal fluid cell counts and protein levels at each post-treatment observation are presented in Figure 8. These findings are essentially similar to those previously reported in asymptomatic neurosyphilis treated with penicillin.[1] Elevated cell counts of 11 or more had practically disappeared by the end of the first post-treatment year. At that time approximately 16% of spinal fluids showed borderline counts of 5 to 10 cells, a number which was reduced to 8% by the end of the fifth post-treatment year. In contrast, elevated protein levels of 51 mg. % or more were present in 19% of spinal fluids at one year and in 10% at five years. Borderline protein levels of 40 to 50 mg. % were present in 24% at one year and in 24% at five years, after treatment.

Since persistently abnormal spinal fluid cell counts of 11 or more were not encountered after treatment of paresis with penicillin, they cannot be correlated with clinical outcome. Borderline cell counts of 5 to 10 were observed in a significant number of patients three years after treatment, at which time clinical progression was recorded in 18% of this group, as compared with only 6% of the group with 0 to 4 cells. Although abnormal and borderline protein levels persisted with much greater frequency than borderline or elevated cell counts, protein levels could not be correlated with clinical outcome. Neither post-treatment cell count nor protein level could be well correlated with post-treatment work status.

Outcome in Relation to Duration of Symptoms at Study Treatment: Figure 9 presents clinical outcome in relation to duration of neurosyphilis symptoms at time of study treatment. Significant numbers of patients have been followed through the fifth year of post-treatment observation. Patients with more recent onset showed, as would be expected, a somewhat more labile process, with more improvement, slightly more progression, and a slightly higher death rate due to neurosyphilis than did patients with longer duration of symptoms at time of treatment.

Fig. 9.—Clinical outcome, by duration of symptoms at study treatment.



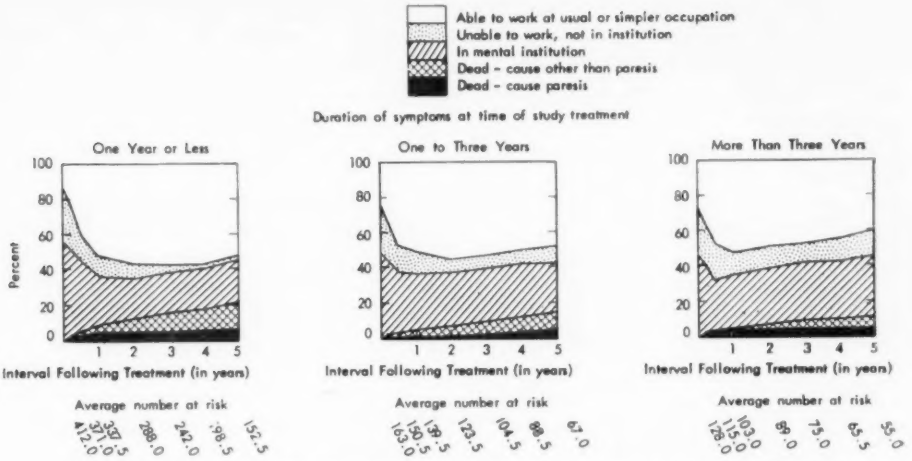

Able to work at usual or simpler occupation
Unable to work, not in institution
In mental institution
Dead – cause other than paresis
Dead – cause paresis
Duration of symptoms at time of study treatment
One Year or Less
One to Three Years
More Than Three Years
Percent
100
80
60
40
20
0
1 2 3 4 5
Interval Following Treatment (in years)
Average number at risk
412.0 327.0 307.0 288.0 242.0 198.5 152.5
163.0 150.5 139.5 123.5 104.5 88.5 67.0
128.0 115.0 103.0 89.0 75.0 65.5 55.0

Fig. 10.—Post-treatment work status, by duration of symptoms at study treatment.

Figure 10 shows post-treatment work status in relation to duration of symptoms at time of study treatment. Significant numbers of patients have been followed through the fifth year of post-treatment observation. At that time results were definitely better for patients with more recent onset. Of those treated within a year of onset of symptoms, 52.4% were working and 24.0% were institutionalized, as compared with 47.4% working and 27.6% institutionalized among those treated one to three years after onset of symptoms, and 39.0% working and 34.1% institutionalized among those treated more than three years after onset of symptoms.

In general, it may be concluded that early diagnosis and treatment afford a significantly increased prospect of clinical improvement, rehabilitation for work, and maintenance in or return to community life.

Outcome in Relation to Previous Treatment: In this study, 56 patients received penicillin prior to study treatment, while 327 patients received no previous treatment and 483 patients received previous treatment other than penicillin. Significant numbers of the last two groups were followed six years after study treatment, at which time 41.5% of previously untreated and 58.4% of previously treated patients had undergone remission or significant improvement. Death due to neurosyphilis had occurred in 6% of the former and in 4% of the latter group. At five years after study treatment 37.2% of previously untreated and 58.7% of previously treated patients were able to work. At this time 39.7% of previously untreated and 21.0% of previously treated patients were in a psychiatric institution.

In view of the large percentage of previously treated patients and of the demonstrably favorable effect of previous treatment other than penicillin, it cannot be said that this study reflects the effect of penicillin alone, but only the effect of penicillin with or without fever therapy on a mixed group of paretics, a significant but undetermined number of whom probably had an arrested process when penicillin first was given. That this detracts from the accuracy of the absolute percentages cited cannot be denied, but that it significantly affects their order of magnitude seems unlikely.

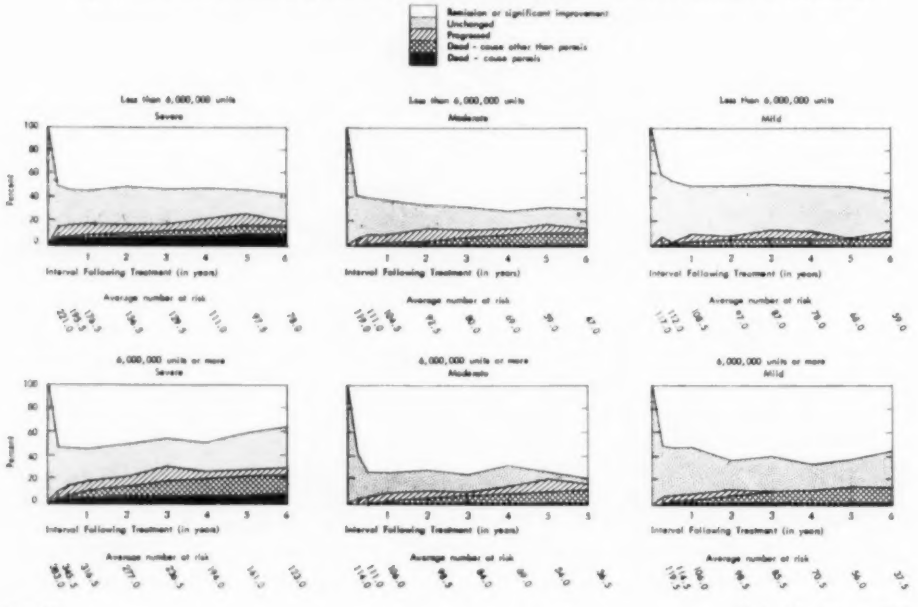
Outcome in Relation to Type and Amount of Treatment at Study Treatment: The present material was not found suitable for a statistically valid comparison of the effects of aqueous and repository penicillin preparations in the treatment of general paresis.

Relatively few patients received the long-acting preparations, and those who did were, of course, an ambulatory group, with only 61.2% of those with severe paresis institutionalized at time of such treatment. In comparison, 85.8% of patients with severe paresis were hospitalized when treated with aqueous penicillin. Too few patients with mild or moderate paresis were treated with repository preparations to permit comparison. Among severe cases a significant number of patients were followed for four years after treatment, at which time a significantly larger percentage were improved than after treatment with aqueous penicillin. It is believed, however, that a large but undetermined factor in this difference was the difference in type of patient treated, rather than the type of penicillin used. It is permissible, however, to conclude that repository penicillin is quite as suitable as aqueous penicillin for the treatment of paresis. This conclusion has been amply borne out by clinical experience with patients treated more recently than those included in the present study.

Figure 11 presents clinical outcome in relation to amount of penicillin (study treatment), by severity of paretic psychosis. Significant numbers of patients treated with less than 6,000,000 units or with 6,000,000 units or more of penicillin have been followed through the fifth to the sixth year of post-treatment observation. Consistent differences between these two treatment groups could not be demonstrated. Consideration of work ability and psychiatric institutionalization in these two treatment groups also failed to reveal consistent differences. These data fit in well with the known extreme sensitivity of Treponema pallidum to penicillin. Although the present study does not permit a statement as to the minimal effective dose of penicillin in paresis, it does support the pragmatically important conclusion that 6,000,000 units is ample.

Outcome in Relation to Penicillin Alone and Penicillin Plus Fever Therapy: A comparison of the effect of penicillin alone with the effect of penicillin plus fever therapy is of practical importance. Unless it can be

Fig. 11.—Clinical outcome, by amount of penicillin (study treatment), by severity of psychosis.



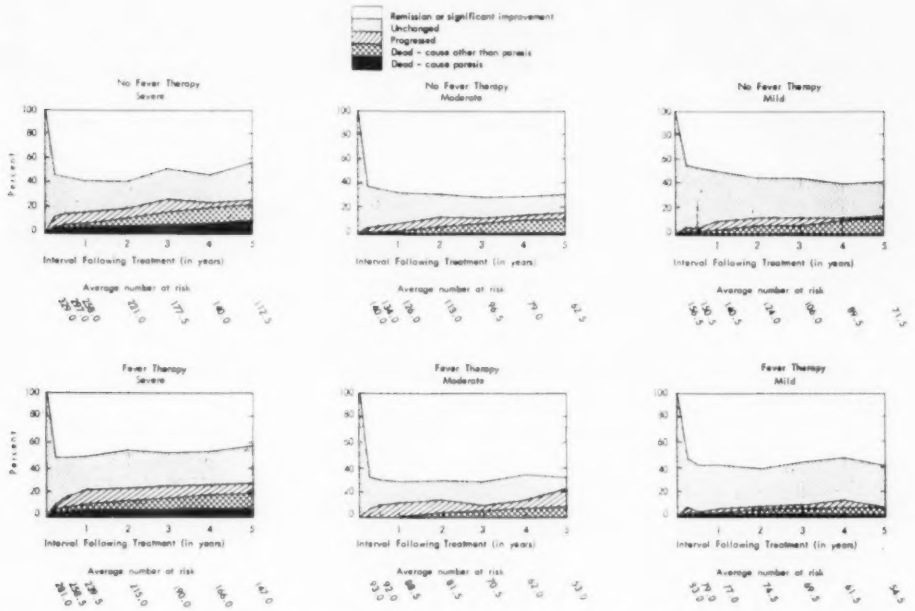


Fig. 12.—Clinical outcome, by type of treatment, by severity of psychosis (penicillin alone and penicillin plus fever).

definitely shown that there is meaningful additive effect, the markedly increased hazards and expenses of the latter form of treatment preclude its utilization. Figure 12 presents the clinical outcome in relation to type of treatment by severity of paretic psychosis. There is no appreciable difference between those receiving penicillin alone and those receiving penicillin plus fever therapy. Significant numbers of patients have been followed through the fifth year of post-treatment observation. At that time the percentages of improved and unchanged status were practically identical for the two therapy groups among the severe, moderate, and mild cases, and actually fewer of those treated with penicillin alone were in a psychiatric institution. Death due to neurosyphilis, limited practically altogether to the severe group, occurred slightly more frequently in those treated with penicillin alone than in those treated with penicillin plus fever therapy.

Figure 13 presents post-treatment work status in relation to work status at time of study treatment, by type of treatment. Patients able to work at time of treatment continued to be able to do so five years later whether treated with penicillin alone or with penicillin plus fever. Patients unable to work but not institutionalized at time of treatment likewise showed no significant difference in work status five years later. Patients institutionalized when treated, who constituted numerically the largest group treated with fever, did better than similar patients treated with penicillin alone, 35%, as compared with 20%, having returned to work five years after treatment. By this time death due to neurosyphilis had occurred in 6% of patients in this group treated with penicillin plus fever and in 10% of those treated with penicillin alone.

In general, as measured by the two yardsticks of clinical mental status and work or institutionalization status, it seems clear that the possible additive effects of fever therapy are not sufficient to justify its use in any significant number of patients. Yet the individual clinician has some grounds

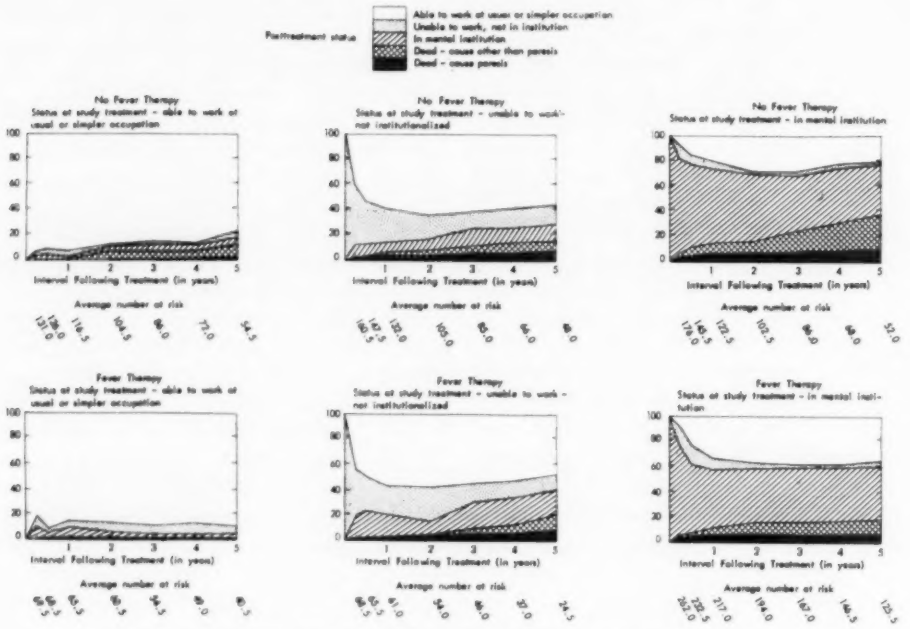

Posttreatment status
Able to work at usual or simpler occupation
Unable to work, not in institution
In mental institution
Dead – cause other than paresis
Dead – cause paresis
No Fever Therapy
Status at study treatment – able to work at usual or simpler occupation
Status at study treatment – unable to work – not institutionalized
Status at study treatment – in mental institution
Fever Therapy
Status at study treatment – able to work at usual or simpler occupation
Status at study treatment – unable to work – not institutionalized
Status at study treatment – in mental institution
Interval Following Treatment (in years)
Average number at risk

Fig. 13.—Post-treatment work status, by work status at study treatment and by type of treatment (penicillin alone and penicillin plus fever).

for its use in selected cases—the somewhat lower death rate due to neurosyphilis in severe or institutionalized patients and the greater rehabilitation for work in the latter group.

Outcome in Relation to Herxheimer Reaction: The incidence and type of Herxheimer reactions have been discussed previously. Of equal importance is the question, repeatedly raised in the past, of possible permanent damage from this reaction. In the present material there is no evidence of such permanent damage. Indeed, remission or significant improvement was present five years after treatment in 70.4% of patients with clinical Herxheimer reactions and in 60.9% of patients with febrile Herxheimer reactions, as compared with 48.8% of patients without Herxheimer reactions. Work status outcome was also somewhat more favorable in the presence than in the absence of a Herxheimer reaction. At five years after treatment, 59.8% of patients with clinical Herxheimer reactions were able to work, as compared with 41.3% and 40.4% of the other two groups, respectively. Only 17.1% were institutionalized, as compared with 29.8% and 31.3%.

These differences may be due in part to the relatively small size of the Herxheimer groups, and in part to the fact that Herxheimer reactions occur with greater frequency in patients with an active inflammatory process in the central nervous system, which has been shown to be more susceptible of improvement by treatment.

Outcome in Relation to Chronic Alcoholism: Since a greater percentage of alcoholics than of nonalcoholics were classified as having severe paresis (although evaluation of severity of paresis in the presence of alcoholism is most difficult), it has seemed best to consider only severe cases. At five years there were no significant differences in clinical or work status between alcoholic and nonalcoholic patients with severe paresis. It seems probable that the presence of alcoholism tended to make the paresis seem severer than it really was and that the added disability due to alcoholism

may have more or less counterbalanced the possible intrinsically lower severity of the paresis in the alcoholic group, thus obscuring any possible differences in outcome.

Outcome in Relation to Educational Level: Significant numbers of patients were followed five years after treatment. Clinical improvement, death due to neurosyphilis, and institutionalization were essentially the same for patients with more than eight years of schooling and patients with eight years or less of schooling. As would be expected, the better-educated patients were somewhat better able to work (48% *vs.* 41%).

Outcome in Relation to Age: Only clinical outcome as estimated by examination of mental status is considered, since work status outcome by age is influenced by numerous irrelevant extraneous factors. Significant numbers of patients in the age groups 30-39, 40-49, and 50-59 years were followed for six years after treatment without significantly different percentages of improvement, but with increased probability of death due to neurosyphilis with increase in age at time of treatment. At six years after treatment, death due to neurosyphilis had occurred in 1% of the 30-39 age group, in 4% of the 40-49 age group, and in 8% of the 50-59 age group. Relatively few patients were less than 30 or more than 60 years of age at time of treatment. In the youngest age group improvement was frequent, but death due to neurosyphilis was disproportionately high, reflecting in large part the presence of a large number (39 of 69 patients) of congenital paretic neurosyphilitics. In patients over 60 years of age at time of treatment, remission or improvement occurred with much less frequency than in any of the younger age groups, a not unexpected finding in view of the frequency of cerebral vascular changes in this age group.

Outcome in Relation to Race and Sex: Only clinical outcome as estimated by examination of mental status is considered, as work status outcome by race and sex is influenced by irrelevant extraneous factors. Significant numbers of patients were followed for six years after treatment without strikingly different percentages of improvement. Nonwhite males did somewhat less well than the other race and sex groups: Improvement occurred in 41.4% of nonwhite males, as compared with 53.5% of white males, 52.1% of white females, and 49.0% of nonwhite females. At six years, death due to neurosyphilis had occurred in 4% of white males, 3% of white females, 9% of nonwhite males, and 6% of nonwhite females.

Signs and Symptoms of Paresis

Since the presence or absence of the more frequent signs and symptoms of paresis was recorded both at time of study treatment and at each post-treatment observation, it

TABLE 7.—*Symptoms at Time of Study Treatment* *

Symptom	Total		Normal		Abnormal	
	No.	Per Cent	No.	Per Cent	No.	Per Cent
Calculation	861	100.00	175	20.3	686	79.7
Insight	947	100.00	194	20.5	753	79.5
Judgment	751	100.00	160	21.3	591	78.7
Retention (delayed)	779	100.00	171	22.0	608	78.0
Speech	986	100.00	223	22.6	763	77.4
Recent memory	983	100.00	236	24.0	747	76.0
Information	780	100.00	229	29.4	551	70.6
Handwriting	317	100.00	103	32.5	214	67.5
Tremors	963	100.00	318	33.0	645	67.0
Remote memory	955	100.00	320	33.5	635	66.5
Unduly depressed or euphoric	995	100.00	370	37.2	625	62.8
Psychotic on simple observation	992	100.00	484	48.8	508	51.2
Logical sequence to conversation	946	100.00	507	53.6	439	46.4
Oriented for time	1,009	100.00	572	56.7	437	43.3
Neatly dressed	597	100.00	371	62.1	226	37.9
Oriented for place	1,007	100.00	642	63.8	365	36.2
Delusions or hallucinations	991	100.00	641	64.7	350	35.3
Oriented for person	908	100.00	760	83.7	148	16.3
Convulsions	988	100.00	890	90.1	98	9.9
Incontinence	919	100.00	831	90.4	88	9.6
Able to dress self, etc.	744	100.00	673	90.5	71	9.5

* Excluded are 26 patients who were senile at time of study treatment.

has been possible to evaluate the effects of treatment on these signs and symptoms individually, a matter of considerable importance to the physician dealing with these patients. Twenty-six patients who were senile at time of study treatment were omitted from this phase of the evaluation.

Frequency of Occurrence.—In Table 7 is shown, for each individual sign or symptom at time of study treatment, the total number of patients for whom such data were available and the percentage of the total number who were abnormal. Table 7 affords valuable quantitative diagnostic information. The most frequent clinical evidences of paresis are impairment of calculation, insight, judgment, retention, speech, and recent memory. Slightly less frequent are tremors and impairment of general information for educational level, handwriting, and remote memory. Mood changes of some degree occur with great frequency. Approximately half the patients are psychotic on simple observation, and a similar number show illogical sequence to conversation. Disorientation, untidy dress, and overt delusions and hallucinations occur with considerably less frequency. Convulsions, incontinence, and inability to dress self and perform other simple acts of personal toilet occur in fewer than 1 out of 10 patients. It can readily be seen that if formal examination of mental status is omitted and sole reliance placed upon simple conversation, observation, or the occurrence of gross psychotic changes, the diagnosis will be missed in approximately 50% of paretics.

Effect of Treatment.—In Table 8 is shown the effect of treatment upon symptoms present at the time of treatment. Significant numbers of patients were followed for five years. It should be clearly stated that in order to avoid, as far as possible, subjective bias and differences between examiners, the "all-or-none" rule was applied, the attempt not being to record improvement but only to note complete disappearance of the sign or symptom in question. In view of this rather stringent interpretation, the effects of treatment upon the symptoms and signs of paresis are in general strikingly beneficent. At five years after treatment, 16 of the 21 individual symptoms studied had disappeared in 45% to 60% of the patients. Abnormalities of affect and disorientation were most frequently benefited; convulsions had disappeared with equal frequency, and tremors and incontinence cleared up surprisingly often. As is well known to the experienced clinician, treatment was significantly less effective in restoring to normal the abnormalities of speech, insight, calculation, general information for educational level, and judgment.

TABLE 8.—*Effect of Treatment on Symptoms Present at Time of Treatment, in Rank Order by Percentage Normal at Five Years After Treatment*

Symptom	No. Abnormal at Time of Treatment	No. Examined at 5 Yr.	Per Cent Normal at 5 Yr.
Disoriented for person	148	50	60.6
Unduly depressed or euphoric	625	280	60.2
Disoriented for place	365	153	59.6
Convulsions	98	38	57.7
Disoriented for time	437	189	56.0
Untidy in dress	226	98	55.3
Tremors	645	288	54.0
Incontinence *	54	14	53.5
Unable to dress self, etc.	71	20	51.0
Impaired remote memory	635	287	49.2
Impaired retention (delayed)	608	270	47.7
Delusions or hallucinations	350	152	47.5
Impaired recent memory	747	350	47.3
Illogical sequence to conversation	439	188	46.5
Impaired handwriting	214	87	45.1
Psychotic on simple observation	508	230	44.7
Impaired judgment	591	267	34.0
Impaired calculation	686	319	31.7
Impaired general information (for education level)	551	250	30.8
Impaired insight	753	326	30.5
Impaired speech	763	340	29.9

* Taboparetics excluded.

Table 9 shows the development of individual symptoms at five years after treatment in those patients without the symptom in question at time of treatment. In most instances these progressions are not believed to represent true biologic progression of the neurosyphilitic process but, rather, are considered to point up differences between examiners in interpretations of what is normal

TABLE 9.—*Development of Symptoms, in Rank Order, by Percentage Developing Symptoms at Five Years After Treatment*

Symptom	No. Without This Symptom at Time of Treatment	No. Examined at 5 Yr.	Per Cent Developing Symptom at 5 Yr.
Impaired calculation	175	97	22.4
Impaired general information (for education level)	229	122	19.8
Impaired retention (delayed)	171	103	14.7
Impaired recent memory	236	119	14.2
Impaired judgment	160	94	13.3
Impaired speech	223	119	13.2
Unduly depressed or euphoric	370	189	11.2
Tremors	318	159	10.7
Impaired insight	194	119	9.7
Impaired remote memory	320	167	9.2
Illogical sequence to conversation	507	254	8.8
Delusions or hallucinations	641	323	7.5
Disoriented for time	572	291	7.3
Impaired handwriting	103	53	6.8
Untidy in dress	371	181	5.2
Disoriented for place	642	326	4.4
Psychotic on simple observation	484	236	4.1
Disoriented for person	760	373	3.3
Incontinence *	661	258	3.1
Convulsions	890	416	2.7
Unable to dress self, etc.	673	327	2.3

* Taboparetics excluded.

and what is abnormal, or progressive dementia on a basis of brain damage antedating treatment. In this connection it is noteworthy that the gross, more easily interpreted factors (convulsions, incontinence, inability to dress self, disorientation, untidiness, psychotic appearance, and impaired handwriting) were rarely recorded as progressions. Calculation and information, which are much more difficult to assess, headed the list of progressions.

Probability of Death After Penicillin Treatment of Paresis

The end-point in untreated paresis, as evidenced by the literature prior to the introduction of malaria therapy by Wagner-von Jauregg in 1917, is death usually within a period of four years from detection. The probability of death after penicillin treatment (with or without fever) is in striking contrast. As shown in Figure 14, the probability of death from paresis is 3.7% at 1 year, 4.9% at 2 years, 6.0% at 4 years, 7.5% at 6 years, 8.7% at 8 years, and 8.9% at 10 years, after treatment. The probability of death from all forms of syphilis is only slightly higher. The probability of death from extraneous causes is considerably greater than the probability of death from syphilis, a rather startling finding in view of the formerly dread nature of paretic neurosyphilis. The probability of death from *all* causes (syphilis included) is 7.7% at 1 year, 11.7% at 2 years, 17.2% at 4 years, 22.8% at 6 years, 27.5% at 8 years, and 31.4% at 10 years.

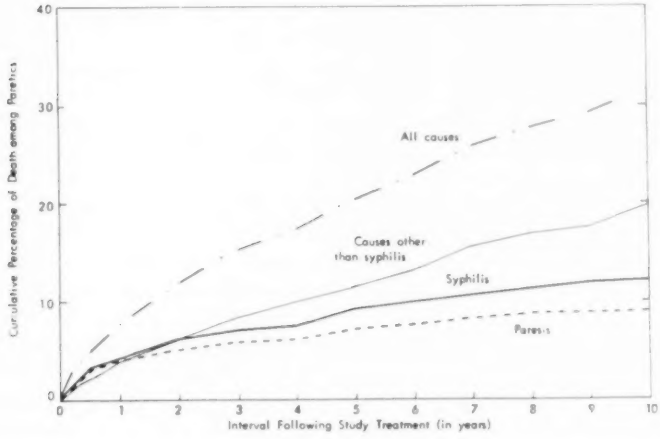


Fig. 14.—Probability of death among paretics after study treatment.

TABLE 10.—*Per Cent Dead Due to Neurosyphilis at Five Years After Treatment*

Symptom	Per Cent Dead at 5 Years (Symptom Absent at Treatment)	Per Cent Dead at 5 Years (Symptom Present at Treatment)
Unable to dress self, etc.	2	19
Incontinence	4	19
Convulsions	4	11
Disoriented for person	3	9
Disoriented for place	2	9
Disoriented for time	2	8
Delusions or hallucinations	2	8
Illogical sequence to conversation	3	8
Psychotic on simple observation	3	7
Untidy in dress	2	7
Impaired handwriting	0	7
Impaired insight	0	6
Tremors	2	6
Impaired recent memory	1	6
Impaired remote memory	2	5
Impaired retention (delayed)	3	5
Unduly depressed or euphoric	3	5
Impaired general information (for educational level)	0	5
Impaired calculation	1	5
Impaired judgment	0	5
Impaired speech	3	5

Not shown in graphic form are comparable probabilities of death for patients who received only one course of treatment, since they are essentially identical with those for the group as a whole. *This essentially identical probability of death rates in those who received one and those who received more than one course of treatment is strong evidence against the necessity for, or value of, routinely repeated courses of penicillin in the treatment of paresis.*

The total role of penicillin-treated paresis as a cause of death is not accurately depicted by any of the curves of Figure 14. In addition to deaths due to neurosyphilis and other forms of syphilis, there is an excess mortality due to other diseases among penicillin-treated paretics as compared with the population at large, doubtless owing to increased susceptibility as a result of varying degrees of debilitation. Somewhere between the curves depicting the probability of death due to syphilis and the probability of death due to all causes lies the true cost of paresis in terms of death.

The difference in death rates between penicillin-treated paretics and a group of nonsyphilitics of similar age, race, and sex has been estimated by computing specific age-race-sex *total* death rates in our study population (number of deaths per 1,000 person-years of observation) and applying them to the 1950 United States population to secure a composite rate adjusted for age, race, and sex. The actual death rate for causes other than syphilis occurring in the United States in 1950 was compared with the adjusted rate for our study group. The death rate per 1,000 per annum was 10.8 for the population as a whole and 37.7 for the penicillin-treated paretic group. It may thus be concluded that the paretic, even though treated with the best available methods, has nearly four times the death rate of his or her nonsyphilitic age, race, and sex counterpart. The best treatment of paresis remains its prevention by the prompt detection and adequate treatment of early syphilis or of asymptomatic neurosyphilis.

Re-Treatment

It was hoped that answers to the questions of when to re-treat, whether to re-treat, and what results to expect from re-treatment might be obtained from the large group of patients available for study.

In a previous section it was pointed out that those previously treated with means other than penicillin seemed to have a more favorable outcome than those previously untreated. Working forward from the reference point of "study treatment," some explanation for this may be forthcoming.

Treatment given to the patient at the time of "study treatment" was the episode that placed the patient in this study. It presupposes judgment of the physician instituting treatment that the patient has paresis, judgment corroborated by supporting clinical and laboratory findings submitted with the abstracts. It presupposes expectation by the physician that value should accrue to treatment, that the course of the disease was then amenable to modification by therapy, i. e., that the disease was active.

However, particularly in the earlier periods, when less was known about penicillin,

some patients presumably "inactive" according to clinicians' reports and spinal fluid findings were given treatment just to see whether any favorable results might be secured. In another section ("Results of Treatment") the outcome of therapy is related to the "activity" at the time of "study treatment." It is obvious that for some patients the very administration of penicillin at "study treatment" represented re-treatment.

The schedule of treatment adopted by some clinics, the University of Pennsylvania in particular, called for repeated courses of therapy at given intervals. For statistical purposes penicillin given subsequent to the first course can be classified only as re-treatment. Even though the patient may have shown satisfactory progress, the scheduled courses were given at the appointed time, as is necessary in a well-designed treatment study.

As will be noted on the follow-up form (Figs. 1E and 1F), there was an opportunity to indicate the reason for re-treatment, including "planned schedule courses," which was to be listed under Heading 9. Thus, it was possible to study in some detail the reasons for re-treatment.

Aside from penicillin given incidentally for other illnesses and from re-treatment administered in accordance with the original plan of treatment, there were essentially two different reasons for re-treatment: (1) clinical progression and (2) insufficient improvement in clinical status or laboratory findings.

In general, re-treatment for clinical progression or for insufficient improvement was given within the first three years after "study treatment." However re-treatment for other reasons, as could be expected from use of penicillin for conditions other than syphilis, was found to occur at any time.

An attempt first was made to study the results of re-treatment in those with mild, moderate, or severe paresis at the time of study treatment with respect to the following factors: race, sex, and age; type of psychosis; previous treatment status; year of treatment; Herxheimer reaction; amount of penicillin; type of penicillin, and use of fever with penicillin. However, detailed analysis of the percentage of patients re-treated as related to the various factors mentioned yielded findings so erratic as not to be susceptible of interpretation.

A second approach to the problem was then made. It was thought that an approach based upon clinical progression might be somewhat more rewarding, in view of the fact that some so-called re-treatment was given as a part of a planned treatment schedule, or for reasons unrelated to syphilis, or for a variety of other reasons.

Information regarding relationship between signs and symptoms at study treatment and re-treatment was available in sufficient detail to give assurance of the validity of the impression of clinical progression as a reason for re-treatment.

Among the 289 patients re-treated after "study treatment," 50 were re-treated for clinical progression. Forty-five of these cases had sufficient follow-up to provide a basis for analysis. It was noted that 14 of this group had shown initial improvement following "study treatment," and that 31 had shown no improvement.

Re-treatment seemed to benefit the 14 patients who had improved after the initial course and subsequently had progressed, so that only 2 of them were dead or institutionalized at latest observation. Re-treatment did not seem to benefit the 31 patients who had not improved after the initial course, as 26 of them were dead or institutionalized at latest observation.

The two groups showed no significant differences in severity of paresis at the time of "study treatment," and no significant difference in spinal fluid activity at time of re-treatment.

It is of interest that all of the 14 patients who had improved after the initial course of treatment did so on a dose of less than 6,000,000 units of penicillin, only subsequent to progress. The paretic process in this group was obviously an active one, being temporarily favorably affected by a subcura-

tive dose and therefore susceptible of being arrested by re-treatment. In contrast, 16 of the 31 patients who had not improved after the initial course of treatment had received 6,000,000 units or more of penicillin, suggesting that in this group the process was advanced and static, and insusceptible of improvement by any amount of additional penicillin.

On the basis of these findings, it appears that the "curative" dose of penicillin in paresis is probably in the neighborhood of 6,000,000 units. If a patient who has received less than 6,000,000 units in an initial course of treatment shows remission of symptoms before onset of clinical progression, re-treatment with a dose in excess of 6,000,000 units will probably be beneficial. But if a patient has received an initial course of 6,000,000 units or more of penicillin, shows no remission of symptoms, and has an inactive spinal fluid, then further treatment in any amount can usually be expected to serve no useful purpose.

Conclusions

1. Repository penicillin is quite as suitable as aqueous penicillin for the treatment of general paresis (dementia paralytica). Although the minimal effective dose is unknown, the present study permits the pragmatically important conclusion that 6,000,000 units is ample.

2. Penicillin prevents paresis. None of the present group of 1,086 patients had received penicillin for early syphilis. Paresis has not been observed to develop after the penicillin treatment of asymptomatic neurosyphilis.

3. The present study cannot be said to reflect the effect of penicillin alone; rather, it presents only the effect of penicillin with or without fever therapy on a mixed group of paretics, a small, but undetermined, number of whom already had a process apparently arrested by other types of therapy before penicillin was given. That this detracts from the accuracy of the absolute percentages cited cannot be denied, but that it significantly affects the order of magnitude seems unlikely.

4. The trend in recent years in the United States has been toward the treatment of general paresis with penicillin alone. The possible additive effects of fever therapy are not sufficient to justify its use in any significant number of patients. The early diagnosis and prompt penicillin treatment of incipient paresis will result in clinical remission and ability to work in more than 80% of patients, and will prevent practically all deaths from neurosyphilis. Even the severely affected or institutionalized patient has 1 chance out of 3 for improvement and rehabilitation for work. In contrast to the dire prognosis of untreated paresis, only 9% of penicillin-treated paretics are dead of neurosyphilis 10 years after treatment. Even so, the penicillin-treated paretic has nearly four times the death rate of his or her nonsyphilitic age, race, and sex counterpart.

5. The effects of treatment upon the individual symptoms and signs of paresis are, in general, strikingly beneficent. In the majority of cases, however, impairments of speech, insight, calculation, judgment, and general information do not entirely disappear.

6. Paresis strikes most frequently during life's most productive years. It is seen approximately three times as frequently in men as in women, and over twice as frequently in white persons as in Negroes. The usual incubation period is 10 to 24 years after infection, with a spread from 2 to more than 30 years. The simple demented type of psychosis is more frequent than all other types combined. In the absence of previous treatment the spinal fluid Wassermann reaction is always positive, usually with small amounts of fluid, and the spinal fluid cell count is almost always elevated. The blood serologic test may rarely be negative.

7. In general, more than one adequate course of penicillin (6,000,000 units or more) is of no demonstrable additional value in the treatment of paresis. Absence

of clinical improvement, persistently abnormal spinal fluid protein level, or persistently positive spinal fluid Wassermann reaction are not indications for re-treatment. Re-treatment with penicillin is indicated under the following circumstances: an initial course of therapy of less than 6,000,000 units, temporary clinical improvement following an initial course with subsequent clinical progression, or spinal fluid cell count of 5 or more after the first post-treatment year. The essentially identical probabilities of death in patients who received one course of treatment and in patients who received more than one is strong evidence against the value of routinely repeated courses of penicillin in the treatment of paresis.

8. Herxheimer reactions, notably exacerbation of the paretic psychosis or convulsive seizures, occur more frequently in the presence than in the absence of spinal fluid pleocytosis. Pretreatment sedation and often the use of anticonvulsants are advisable. The Herxheimer reaction does not cause long-term damage in paresis.

9. The diagnosis of paresis will frequently be missed if formal pretreatment examination of mental status is omitted. Indeed, it may be stated that skilled neuropsychiatric examination affords definite prognostic data as to the probability of improvement in psychosis, rehabilitation for work, and, to a certain extent, death itself.

10. Progression and death due to neurosyphilis occur almost altogether in patients with severe pretreatment psychoses. Post-treatment psychiatric hospitalization is directly proportional to, and clinical improvement and rehabilitation for work are inversely proportional to, the severity of pretreatment psychosis. Type of psychosis is of less importance prognostically than is severity of psychosis. The shorter the duration of paretic psychosis at time of treatment, the more frequent is clinical improvement and rehabilitation for work.

11. The presence at time of treatment of incontinence, inability to dress self and perform other simple acts of personal toilet, and, to a less extent, of convulsions, affords a particularly poor prognosis for longevity.

12. Work status at time of treatment is of great prognostic import. Of perhaps equal significance is the length of time which has elapsed since the patient has been able to work at his usual occupation.

13. Age within the limits of 30-59 years, race, and sex are relatively unimportant factors in the prognosis of paresis.

14. Pretreatment pleocytosis indicates an active inflammatory process more susceptible of improvement by treatment, but in a minority of cases leaving behind sufficient brain damage to nullify any real clinical effect. The absence of pleocytosis indicates a relatively static process less susceptible of improvement but, at the same time, less likely to progress. Pretreatment spinal fluid protein levels are of less prognostic import.

Persistent cell counts of 11 or more were not usually encountered after penicillin treatment. Clinical progression did, however, occur significantly more frequently with persistent cell counts of 5 to 10 than with cell counts of 4 or less. Persistent spinal fluid protein elevations were relatively frequent, but of no prognostic import.

The Johns Hopkins Hospital.

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Reticulum-Cell Sarcoma of Brain (Microglioma)

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Primary sarcoma of the brain is rare, having been estimated to comprise only 0.25% of all intracerebral neoplasms.[1] The relative paucity of recorded cases, as well as the uncertain nosologic position of some glial cells, has apparently impeded their precise classification. The various appellations utilized for some intracerebral sarcomas with similar morphologic features and biologic behavior have further complicated the study of this group of neoplasms. The recent studies of Feigin and associates[2,3] have satisfactorily demonstrated the vascular origin of that form of sarcomatous growth observed in some glioblastomas. However, much debate has occurred concerning that form of malignant mesoblastic cerebral neoplasm most commonly referred to as microglioma, or reticulum-cell sarcoma. Since the studies of Hortega[4] and, subsequently, Dunning and Furth[5] have indicated that the microglial cells represent the reticuloendothelial elements of the central nervous system, it would appear that much of the controversy concerning this group of tumors has been largely semantic in nature.

The purpose of this report is to describe the morphologic and tinctorial features of two cases of intracerebral sarcoma which warrant their designation as reticulum-cell sarcomas of the brain, or microgliomas. Necropsy in one case revealed the neoplasm confined to the brain, whereas in the second case similar neoplastic tissue was present in one testis. This latter finding prompted us to apply the various stains employed for the identification of microglial cells to several examples of extracerebral reticulum-cell sarcoma.

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Report of Cases

CASE 1.—The patient, a 34-year-old white man, entered the hospital eight days prior to death with the chief compliant of persistent intense bilateral headache of six weeks' duration. The loss of 20 lb. in weight and slight impairment of memory had been experienced since the onset of symptoms.

Physical examination revealed a disoriented, poorly nourished man, in acute distress. The vital signs were normal. There was slight ptosis of the left eyelid, and the disk margins of both fundi were blurred. He was unable to perform simple calculations. He exhibited a staggering gait and a positive Romberg sign to the left. The finger-to-nose test was performed poorly with the left hand. Paresis of the left arm was evident. There was a decrease of superficial pain sensation over the right trigeminal nerve and questionable weakness of the left facial nerve. The deep tendon reflexes were normal, and no pathologic reflexes were elicited.

Laboratory studies revealed hemoglobin 14 gm. per 100 cc.; hematocrit 47%; WBC 9,700/cu.mm., and a normal differential count. Urinalysis showed a trace of sugar and 1+ acetone. Serologic tests for syphilis were negative. Blood chemistry and spinal fluid examinations were within normal limits.

Bilateral carotid angiograms suggested a space-occupying lesion in the right frontoparietal area. A ventriculogram confirmed the presence of the right frontal mass, and also signs indicating involvement of the right thalamus and basal ganglia.

A subtotal right frontal lobectomy was performed, and an infiltrating neoplasm was found to involve the right frontal lobe and the rostral portion of the right basal ganglia.

The patient died 48 hours after the operation.

The surgical specimen consisted of several soft fragments of brain tissue, together measuring 1.0×0.5×0.5 cm., and a large, irregular mass of brain tissue measuring 6.0×4.5×4.0 cm. and weighing 35 gm., which on section was firm, homogeneous, and gray-white.

Necropsy.—Gross Sections: At necropsy the significant pathologic findings were limited to the brain. The brain weighed 1,750 gm. and contained a surgical defect measuring 5.0×4.0×4.0 cm.

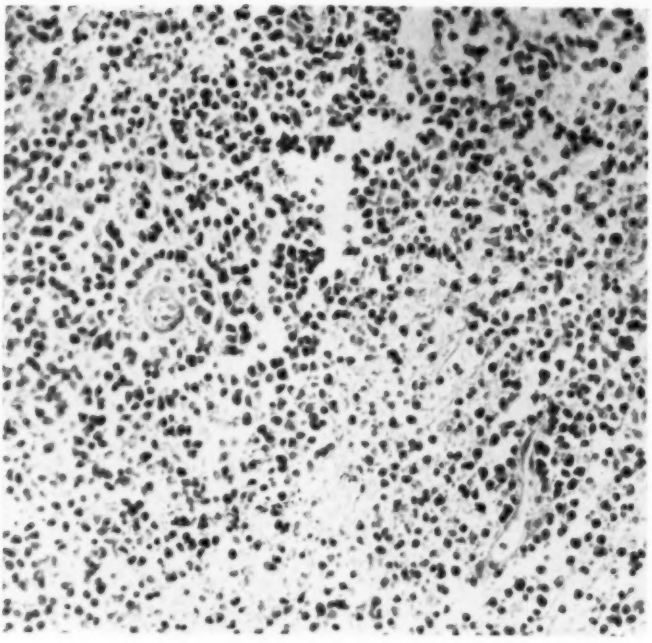

Fig. 1 (Case 1).—Low-power appearance of reticulum-cell sarcoma of brain. × 200.

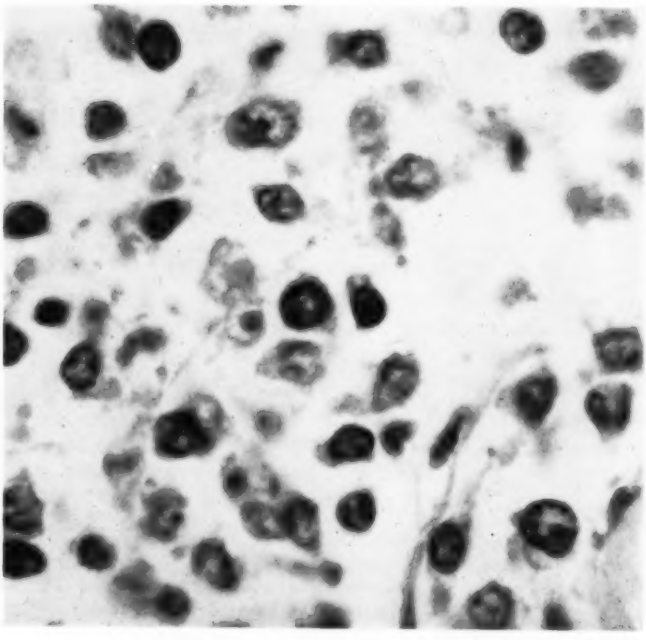

Fig. 2.—Higher magnification of neoplasm depicted in Figure 1, revealing cytologic detail. × 1,200.

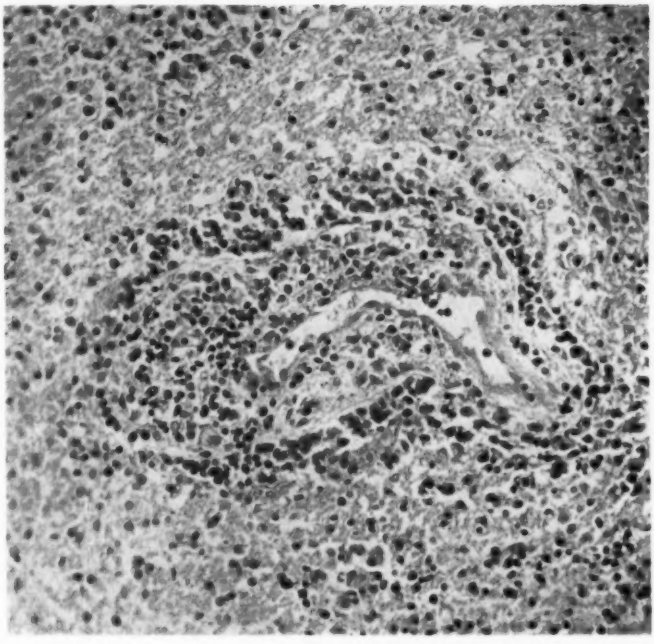

Fig. 3 (Case 1).—Focus of reticulum-cell sarcoma about cerebral vessel remote from main tumor mass. × 185.

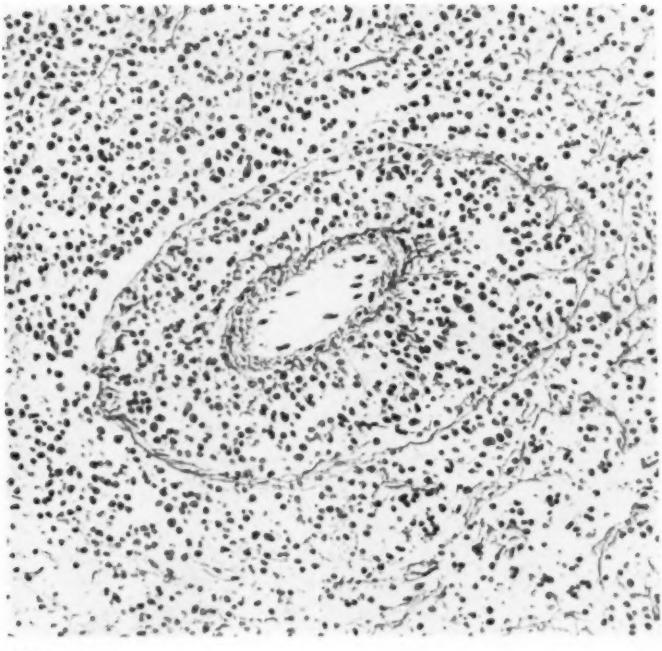

Fig. 4 (Case 1).—Fragmentation of vascular reticulum by neoplasm. Reticulum fibers are also apparent about clusters or large groups of tumor cells. Wilder reticulum stain; × 200.

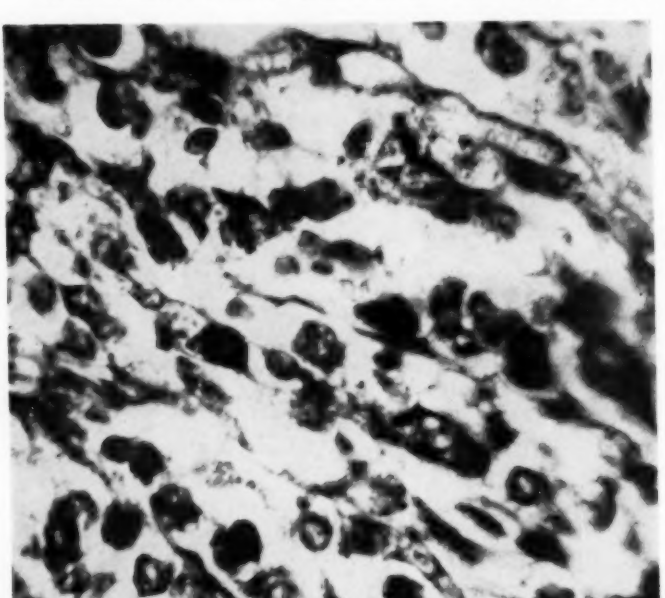

Fig. 5 (Case 1).—Argyrophilic cytoplasms and processes of tumor cells. Weil-Davenport stain; ×1,200.

in the right frontal lobe. The cerebral convolutions were flattened and the sulci narrowed. There was a moderate "pressure cone" of the cerebellar tonsils. After fixation in 10% formalin, coronal sections disclosed homogeneous, gray-white tumor tissue, infiltrating the right putamen and caudate nucleus and extending anteriorly to the rostral portion of the thalamus.

Sections of formalin-fixed tissue were stained with hematoxylin and eosin, the Verhoeff-Van Gieson method, phosphotungstic-acid hematoxylin, Wilder's reticulum stain, and the Weil-Davenport microglial technique.[6] Frozen sections of wet formalin tissue were stained by Penfield's method for microglia.[6]

Microscopic Findings: Microscopic examination revealed a cellular neoplasm formed by round and oval cells, containing a small amount of cytoplasm and a single round to oval nucleus (Fig. 1). The latter was frequently vesiculated, with prominent nucleoli, and the nuclear chromatin was arranged in a delicate network. An occasional nucleus was indented or lobulated (Fig. 2). A moderate number of atypical mitoses were noted. A conspicuous feature of the neoplasm was the perivascular cuffing and the obliteration of the Robin-Virchow spaces. The tumor cells in areas split the adventitial covering of the vessels; however, the vascular endothelium was intact. Sections of the brain stem and contralateral frontal and occipital lobes disclosed small focal collections of tumor cells surrounding the cerebral vessels (Fig. 3).

Sections stained by the Wilder reticulum method revealed delicate fibers about clusters of tumor cells, but no distinct relationship to individual cells within the tumor. The perivascular and mural reticula of the cerebral vessels were split by neoplastic cells presenting a distinctive appearance (Fig. 4).

Sections stained by microglial techniques revealed the majority of cells to contain argyrophilic material within their cytoplasm (Fig. 5). In addition, a number of cells possessed branching cytoplasmic processes.

The phosphotungstic-acid-hematoxylin stain showed no fibrils arising from the tumor cells. Sections stained for elastic fibers were not abnormal.

Case 2.—The patient, a 33-year-old white man, entered the hospital 22 days before death complaining of persistent vomiting, of nine days' duration. A craniotomy had been performed four years previously for a right frontal lobe tumor at another hospital. A diagnosis of glioma, type undetermined, was made. After operation he received x-ray therapy and maintenance doses of diphenylhydantoin (Dilantin) and phenobarbital. He had done well on this regimen and was able to engage in his usual activities until the onset of his present illness.

Physical examination revealed a slightly obese white man in no acute distress. He was cooperative, oriented, and alert. A healed right frontoparietal scar was present. There was horizontal and rotary nystagmus on left lateral gaze. No papilledema was present. Neurological examination revealed the cranial nerves to be intact. Tests of cerebellar function, motor strength, and sensation were within normal limits. No abnormal reflexes were elicited.

Laboratory tests revealed hemoglobin 15 gm/100 cc.; WBC 12,000/cu.mm., with a normal differential count. Serologic tests for syphilis were negative. An electroencephalogram showed slow activity in the right frontal lobe, with spread on occasion to the right temporal lobe.

X-ray of the skull demonstrated the previous operative defect. A carotid angiogram revealed the anterior cerebral arteries to be in the midline.

A craniotomy was performed and revealed a neoplasm involving the right frontal and right temporal lobes. Postoperatively the patient was confused, developed Jacksonian seizures, and died seven days after operation.

The surgical specimen consisted of several firm, irregular, pink-gray fragments of tissue, together measuring 0.6×0.3×0.2 cm.

Necropsy.—Gross Findings: At autopsy the principal pathologic findings were limited to the brain, right testis, and stomach. The brain weighed 1,250 gm. The convolutions were flattened. There was a round defect in the right frontal lobe, measuring 2.5 cm. in diameter. Its wall was granular and yellow. After sectioning, this defect was noted to communicate with the right lateral ventricle, right caudate nucleus, and the anterior limb of the right internal capsule. The posterior aspect of the right lateral ventricle was filled with a cast of pale-gray tumor tissue.

The right testis weighed 50 gm. It was firm. The cut surface was glistening gray-white. The tunica albuginea was intact, and the spermatic cord was not remarkable. The left testis weighed 15 gm. and was soft. Its cut surface was yellow-tan.

The stomach showed a circumscribed ulcer, measuring 1.0 cm. in diameter, situated along the lesser curvature 4.0 cm. from the pylorus.

Microscopic Findings: Sections of the brain and right testis were stained by the same methods as those employed in Case 1.

Microscopically, the cerebral neoplasm was composed of round cells containing a small amount of granular cytoplasm. The individual nuclei were large, vesiculated, and contained prominent nucleoli. Atypical mitotic figures were frequent. Perivascular infiltration within the main tumor mass, as well as sections of brain from uninvolved areas, were similar to that noted in Case 1. Microglial stains revealed the deposition of argyrophilic granules within many tumor cells and the presence of branching cytoplasmic processes.

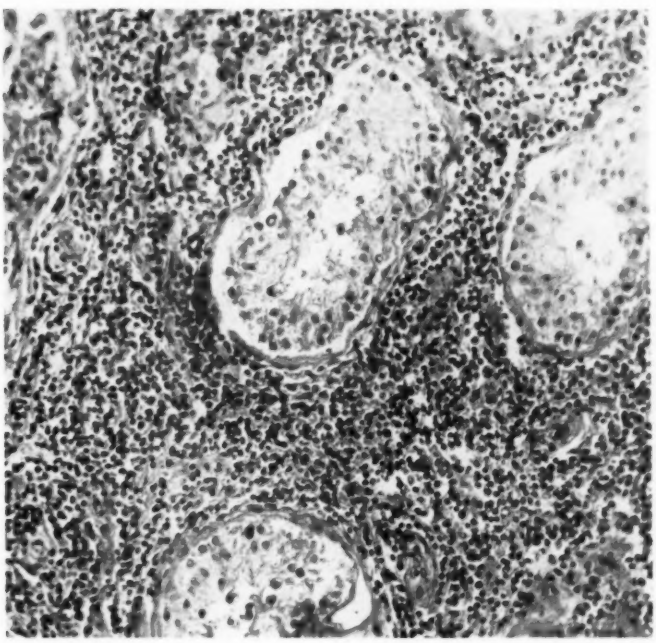

Fig. 6 (Case 2).—Testis revealing infiltration of neoplasm between seminiferous tubules. ×165.

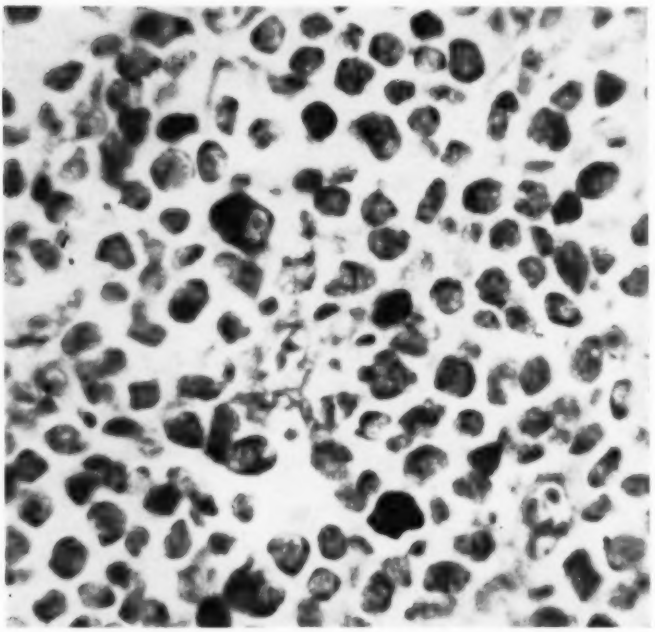

Fig. 7.—Section from extracerebral reticulum-cell sarcoma, revealing argyrophilic cytoplasms. Weil-Davenport stain; ×1,200.

The section of testis showed atrophic tubules separated by numerous neoplastic cells, morphologically identical with those comprising the cerebral tumor (Fig. 6). A similar distribution of reticulum fibers was also noted. Many of the neoplastic cells contained argyrophilic cytoplasms in sections stained by the microglial techniques.

Three unequivocal examples of extracerebral reticulum-cell sarcoma were stained by the Weil-Davenport and Penfield techniques. The cytoplasm of these cells was, for the most part, colored by these microglial techniques (Fig. 7).

Comment

The morphologic and tinctorial features of the cerebral neoplasms observed in the cases presented are similar to those of previously recorded examples of microglioma, reticulum-cell sarcoma, or perithelial sarcoma of the brain. The round and ovoid cells with regular or lobulated and indented vesicular nuclei and frequent, prominent nucleoli are reminiscent of microglial and reticulum cells. The demonstration of cytoplasmic argyrophilia in many of the tumor cells establishes their microglial nature. Those neoplastic cells which do not exhibit this tinctorial property are morphologically unlike those encountered in other gliomas. In addition, the neoplasms lacked neuroglial fibers. These considerations militate against the possibility that the neoplasms presented represent another type of glioma in which microglial infiltration represents a conspicuous feature, although such an event, as emphasized by Penfield,[7] Hsü,[8] and Abbott and Kernohan,[9] may occur. The crux of the debate concerning the nomenclature of these neoplasms has been the identification of the neoplastic cells which fail to exhibit cytoplasmic argyrophilia. Russell and associates [10] considered them as anaplastic forms of the mature, argyrophilic microglial cell, although they indicated the possibility that they may represent progenitors of microglia, reticulum cells. The latter interpretation, if correct, would warrant the designation of these neoplasms as reticulum-cell sarcoma. Since many of the tumor cells exhibit morphologic and tinctorial features identical with those of reticulum cells and their derived neoplasms elsewhere, we have chosen to refer to these tumors as reticulum-cell sarcomas, with a parenthetical ref-

erence to their identifiable microglial component. This concept is in keeping with the generally held histogenetic view that histiocytes (microglial cells) are derived from reticulum cells.

The distribution of reticulum fibers in cellular areas of the neoplasms was variable, although an over-all estimation would indicate an increase of such structures. It is to be noted that these fibers were not disposed about individual cells in the prescribed classical manner of reticulum-cell sarcoma.[11] However, the latter has not been a frequent occurrence in our experience with this type of lymphoma, particularly in extranodal sites. On the other hand, the separation of vascular reticulum by neoplastic cells appears distinctive and assists in the recognition of this type of glial tumor. This configuration has prompted its designation as perithelial sarcoma.[12] The presence of tumor cells about vessels at sites distant from the main tumor mass also represents a characteristic feature of the reticulum-cell sarcoma (microglioma) of brain. The demonstration of this feature would appear to be in large part fortuitous, depending upon the opportunity to examine grossly uninvolved areas of brain. It cannot be stated with certainty whether such deposits represent metastatic spread or multicentric tumor growth. However, the latter appears plausible when it is appreciated that both reticulum cells and microglia are embryologically derived from perivascular sheaths. The marked endothelial hyperplasia and distinctly fibrosarcomatous appearance and identification of other neoplastic elements in those glial sarcomas associated with some examples of glioblastoma multiforme allow for their differentiation from reticulum-cell sarcoma. It is cogent to note, however, that their site of origin, vascular endothelium, links these tumors with the reticuloendothelial system. Further, many consider the fibrocyte a cell type of the second generation derived from reticulum cells.

The occurrence of morphologically identical neoplastic cells in the testis in Case 2 is not an unprecedented finding in this type of glial sarcoma. Russell and associates[10] observed extracerebral foci in three of seven cases. They considered this to conform with the concept of generalized reticulosis, as advanced by Robb-Smith.[13] Some of the extracerebral deposits observed by them contained cells with argyrophilic cytoplasm, a feature which is similar to our findings in the testicular lesion observed in Case 2 and the three unequivocal examples of extracerebral reticulum-cell sarcoma studied.

The clinical course of previously recorded examples of this type of glial neoplasm has been rapidly fatal, the longest survival being recorded as one and one-half years.[11] Case 1 of this presentation exhibited such a fulminant course. On the other hand the other case presented appears unique in that the patient survived approximately four years following initial operative intervention. It appears possible that this more protracted course was in large part due to the x-ray therapy which this patient received, since such a therapeutic response is exhibited by some neoplasms of similar nature arising in other sites.

Summary

Two examples of reticulum-cell sarcoma (microglioma) of brain are presented. Necropsy revealed the neoplasm to be confined to the brain in one, whereas in the other a neoplastic focus with identical morphologic and tinctorial features was observed in one testis.

Identification of this type of glial sarcoma is facilitated by the morphologic similarity of the tumor cells to reticulum cells or histiocytes, the affinity of many cell cytoplasms for those stains employed for the recognition of microglial cells, their characteristic splitting of perivascular sheaths, and the presence of similar neoplastic elements about vessels remote from the main tumor mass.

Although the clinical course of patients with reticulum-cell sarcoma (microglioma)

of brain has been fulminant, attention is directed to a protracted course exhibited by one of the patients presented who had received radiation therapy.

Since the neoplastic cells of this form of glial sarcoma exhibit morphologic and tinctorial features like those of extracerebral reticulum-cell sarcoma, this designation is retained for this type of neoplasm. It is considered that much of the debate concerning these tumors has largely been semantic in nature.

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News and Comment

ANNOUNCEMENT

The ARCHIVES OF NEUROLOGY AND PSYCHIATRY was first published in 1919. At that time neurology and psychiatry were considered related subject fields and it was thought one journal would serve both adequately.

Over the years, psychiatry has been emerging as a distinct specialty. The volume of literature has increased to such an extent that official publications reporting psychiatry either could not absorb it or felt the need to condense the material to accommodate more contributions. Psychiatrists began to feel also that the ARCHIVES OF NEUROLOGY AND PSYCHIATRY should allot more space to psychiatry, that its emphasis over the years had been neurological.

In July, 1956, an effort was made to give equal emphasis to both neurology and psychiatry by dividing the ARCHIVES OF NEUROLOGY AND PSYCHIATRY into a two-section journal, with an editorial board for the Section on Neurology and a separate board for the Section on Psychiatry. This division had the effect of reducing the number of pages devoted to neurology, and the result was late publication dates for accepted articles, with the natural development of a large backlog. More psychiatric manuscripts were now submitted to the ARCHIVES, and only very high editorial standards and a high rate of rejection prevented a large backlog from forming.

The final development is to publish two separate journals. The division is prompted by the demand by both neurologists and psychiatrists for more text pages; by the neurologists, who feel the quality of a journal devoted exclusively to neurology can be much improved, and by the psychiatrists, who believe it is more realistic to recognize neurology and psychiatry as distinct clinical specialties. Consequently, July, 1959, will see the introduction of these two journals—the *A. M. A. Archives of Neurology* and the *A. M. A. Archives of General Psychiatry*.

Books

Mental Symptoms in Temporal Lobe Epilepsy and Temporal Lobe Gliomas. By Torsten Bingley. Acta psychiatrica et neurologica, Supp. 120. Price, not stated. Pp. 151. Ejnar Munksgaard Forlag, Norregade 6, København, K, 1958.

A great deal has been written on the temporal lobe in recent years; but because of a confused nomenclature, it has been hard to understand the exact meaning of many of the authors. Dr. Bingley is to be congratulated on having written a clear and well-thought-out monograph. He gives an excellent historical background of our knowledge of the temporal lobe, paying due respect to Hughlings Jackson and the other great figures in early English neurology. He describes temporal lobe epilepsy extremely well and gives a good classification of the various types of seizure that are found in this disorder. He divides them into Jacksonian fits; perceptual seizures of smell, taste, hearing, and vision; visceral motor and sensory seizures; aphasias; automatisms, and complex mental seizures. His material consists of 90 cases of temporal lobe epilepsy seen in the neurological clinic, all personally studied by careful methods. In addition, there were 253 cases of glioma of the temporal lobe that were seen in the neurosurgical clinic.

His first interest was in finding out the relationship of the symptoms to the handedness of the patients. He believes that handedness is a Mendelian trait with incomplete penetrance. The use of genetic data in diagnosing handedness or in differentiating between left-handed persons with crossed aphasia and those with uncrossed aphasia is possible only if the series compared are fairly large. In his series of 90 cases of temporal lobe epilepsy he found the incidence of left-handedness to be about 6.7 per hundred. He could find no clear evidence that the risk of aphasia following a unilateral lobe lesion is significantly higher in left-handed than in right-handed patients. His observations show that right-brainedness occurs in about 1% of right-handed persons.

Chapter IV discusses the mental symptoms of temporal lobe tumors. It goes extensively into the history of the subject, but most important are the investigations of Bingley himself. There was found to be a constant relation between the presence of raised intracranial pressure and mental symptoms, and the evidence indicated that raised intracranial pressure per se may produce mental symptoms but local destruction of the dominant lobe is likely to produce mental symptoms before the effect of raised intracranial pressure appears. Tumors in the dominant temporal lobe show a stronger tendency to produce mental symptoms, especially intellectual impairment, than do tumors in the recessive lobe.

Chapter V gives a remarkably good description of the ictal mental symptoms of temporal lobe epilepsy. He discusses aphasia, speech automatism, and ictal emotional states, especially anxiety, anger, and euphoric states.

Under automatisms he discusses the masticatory seizures, in which the patient shows licking, spitting, chewing, tasting, and smacking movements. These appeared in 27% of the patients who had a unilateral temporal lobe focus. In 14 of 17 patients with masticatory seizures there was also automatic behavior. This automatic behavior is remarkably well described. As this author uses the term "automatism," it seems to be a much more definitive, and therefore better, name for this type of seizure than "psychomotor seizure," as usually applied in America.

In Chapter VI he gives an excellent description of the mental symptoms that appear between attacks in patients with temporal lobe epilepsy. This includes personality changes, which were assessed by various psychological tests.

For any neurologist or psychiatrist interested in the strange emotional states, dream states and types of rage and euphoria found in patients with temporal lobe lesions, this monograph is very important reading. It shows how difficult it is at times to make a differential diagnosis between, on the one hand, anxiety and the emotional states which arise on a psychogenic basis and, on the other hand, those which are caused by lesions of the temporal lobe.

STANLEY COBB, M.D.

SECTION ON
PSYCHIATRY

The Pathology of Schizophrenia

A Historical Survey

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I

"The fact is decisive that the morbid anatomy [of dementia precox] has disclosed not simple inadequacy of the nervous constitution but destructive morbid processes as the background of the clinical picture." This remark of Kraepelin's[1] immediately reveals the pronounced neuropathological bias with which schizophrenia was received during the early years of this century.

This position on the part of the psychiatrists of the day was, however, not untenable, as Alzheimer[2] had by then reported severe changes in the cerebral cortex, with disorganization of the ganglion cells and extensive glial reactions. He described not only swollen nuclei and shrunken neurons, with a frequent falling out of groups of cells, but also proliferative fibrous gliosis and pigmentary changes. He concluded that these changes were responsible for the disturbance in cortical function of these patients.

It is worth noting that most of these histopathological descriptions applied to brains of catatonic schizophrenics. "There is in catatonia, no doubt, a pathological glial fibrosis in the cortex, limited to certain cortical areas." In a subsequent paper, reviewing the pathological anatomy of 55 cases of dementia praecox, Alzheimer[3] indicated the changes to be more pronounced in Layers II and III of the cerebral cortex.

Here he described the "amoeboid glia" encountered in six of his acute cases. He also remarked that sclerosis of the ganglion cells was practically always associated with varying degrees of lipid degeneration. He concluded that though a histopathological examination may be diagnostic of dementia praecox, any correlation of the site of maximum changes with the clinical type of schizophrenia still appeared unwarranted.

Bleuler[4] also thought there was an "organic" basis to schizophrenia. He said: One must acknowledge that at least the great majority of clinical pictures which are now collected under the name of dementia praecox rests on some toxic action or anatomical process which arises independently of psychic influences. . . . The principal group, in my opinion, is certainly caused by organic changes.

While the majority of early workers had satisfied themselves by confining the neuropathology of schizophrenia to Layers III and V of the cerebral cortex, and by merely commenting on the relative sparing of the motor, sensory, and psychosensory areas,[5] Southard[6] went to the extent of correlating the psychological disturbances of schizophrenia with neuronal and glial lesions of

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the "supracortex" (upper cortical layers). He then proceeded to correlate lesions of the "infracortex" of the temporal and parietal lobes with auditory hallucinosis and catatonia, respectively.

Reviewing his personal histological observations on methylene-blue-stained sections of brains of eight schizophrenics, Mott [7] remarked on the extension of "degenerative cell changes" to the whole brain, including the cerebellum in two cases. He postulated two types of neuropathology: (1) a "congenital arrest of many neurons," especially of the smaller pyramidal cells of the frontal lobe, followed during adolescence by a "widespread neuronic degeneration," and (2) the latter process alone. In both nervous and reproductive (*vide infra*) tissues he felt the essential histological morbid change to be one of "nuclear decay" at the biochemical level. A number of nuclei of the affected cells show, he wrote, "in varying degrees of intensity, a biochemical change by the fact that the nucleoli, which in normal cells are stained a deep blue (basi-chromatin reaction), are stained purple or even reddish-pink (oxy-chromatin reaction)," signifying a diminution of organic phosphorus, which loss may be associated with reduced function of the oxidative processes. As further evidence of hypofunction of neurons, he adduced the presence of intracytoplasmic lipid granules (mostly in the medium-sized pyramidal cells) in suitably stained frozen sections.

Gurd,[8] while attempting a correlation of the duration of schizophrenia with the "lesions" in the brain, noted what she considered more "extreme" changes in two subjects with psychotic symptoms who died in acute catatonic excitement than in others with longer histories. In these two cases, she described the usual degenerative changes in the neurons and the glia, with emphasis on nuclear pallor and pyknosis and severe "fatty degeneration" of glia and nerve cells. In two others, with a duration of two to four years, she was impressed by the chromatolysis and sclerosis of medium-sized pyramidal cells. In 15 subjects with a history of psychosis of 10 to 35 years (and dying at ages between 32 and 63), regressive glial proliferation predominated. She postulated that schizophrenia was a disease with a special localization in the central nervous system and causing degenerative changes that might be continuous or intermittent, corresponding to remissions in the clinical picture.

The first word of caution regarding the interpretation of these diverse neuropathological observations came from Adolph Meyer,[9] who said: "I doubt whether many of us would dare to make our diagnosis from sample sections of the nervous system," and called for some sort of experimental control on these "heterogeneous" anatomical findings.

Josephy [10] not only took critical note of the lack of mention (in histopathological publications) of the age or of the terminal intercurrent disease of the schizophrenic subjects but also suggested that brains be examined and results recorded and grouped independently of clinical findings. He summed up the then current knowledge of the subject by stating that when one speaks of the histopathology of schizophrenia, "one already takes for granted what remains to be proven—namely, the unity of the entire concept."

It is interesting to note that in the description of his own pathological material (brains of 50 schizophrenics and of 5 tuberculous subjects), Josephy utilized controls but could not avoid coming to the same conclusion as most of his predecessors, that there is a specific histological picture for schizophrenia, consisting of an "exfoliation" of the nerve cells of Layers III and V of the frontal cortex, independent of the blood vessels or the choroid plexus [11] of the brain and without conspicuous intrinsic reactions of the neuroglia.

Quite early in this search for the structural substratum of dementia praecox, other systems of the body also came in for their due share of recognition. Thus, Emerson,[12] reporting on 208 "definite schizophrenics" at the Bellevue Psychopathic Hospital, found

61 (29.3%) of these to manifest "typical status lymphaticus." (He found the evidence of this condition among psychoneurotics to be 24%, and among alcoholics and drug habitués to be 22%.) His diagnostic criteria of status lymphaticus were almost entirely restricted to signs of hypogonadism.

More interest, however, was aroused by, and more attention subsequently paid to, the observations of Mott [13] on the testis. On the basis of histological sections of testes obtained from 22 schizophrenics, he described three stages of "regressive atrophy." In the first stage, he saw poor nuclear staining, fewer spermatocytes, and more degenerated spermatozoa—and some smaller tubules with a thickened basement membrane—than in normal testes (though there is no mention of any concurrent normal, control studies). In the second stage most of the seminiferous tubules were found atrophic, with spermatogonia and spermatids but almost no spermatozoa, and an abundant proliferation of interstitial tissue, leading to the third stage, of almost total fibrotic atrophy of the testis.

Under the title of "Constitutional Factors in Dementia Praecox," Lewis [14] published one of the most extensive postmortem reports in the field, with emphasis on the cardiovascular and endocrine systems. In a group of 4,800 autopsies on mental cases at St. Elizabeths Hospital (Washington, D. C.), we are told that the diagnosis of "dementia praecox" was clinically certain in 601 cases. However, only the lethal lesions and cardiovascular changes being described in these, detailed examinations were made in an additional 22 cases, and this material comprises the bulk of the monograph.

Lewis recorded "two outstanding organic features" present universally, and irrespective of all other considerations of the subject's physical condition or of his psychosis, viz., (1) an aplastic circulatory system, and (2) disorders of the thyroid, adrenals, and gonads.

The aplastic cardiovascular system was characterized by a small heart (average weight in 95 cases, 254 gm.), believed to have been arrested in its development at the pubescent stage and free from gross lesions. In support of this, Lewis gives us descriptions and photographs of aplastic aortae also. The lumen of the aorta is said to be narrow; the adventitia and media are shown to be appreciably thinner with normal but small-sized muscle fibers, with subendothelial proliferation of elastic tissue, and a conspicuous absence of atherosclerosis. This feature of smallness and hypoplasia is said to extend throughout the vascular tree and to be associated with hyperplasia of the lymphatic system,[12] with notable increase in inguinal, tonsillar, and pharyngeal lymphoid tissue and overdevelopment of the lymph nodes of the mediastinum and of the intestinal tract.

In the field of endocrine glands, Lewis partly confirmed the observations of Mott and others by describing both gross and microscopic changes of testicular atrophy, with diminution or absence of spermatozoa. He failed, however, to find any correspondence between the severity of the testicular atrophy and the duration of the mental symptoms. Almost as often as there was gonadal regression, he found changes in the adrenal cortex affecting all the three layers and varying from gross atrophy to microscopically detectable fibrous proliferation. In 7 of the 22 cases the adrenal medulla shared in the atrophic process. Of the 21 thyroid glands examined, 7 were found to be unusually small; 9 were smaller than average, and 2 were enlarged, all of them exhibiting the generalized interstitial fibrosis found in other endocrine glands. There was an accompanying loss of colloid in the thyroid, and a tendency in alternating areas to epithelial-cell proliferation and the formation of new, distorted acini. Nearly half the number of cases also showed some replacement of cells by connective tissue in the anterior and posterior lobes of the pituitary. In six instances the basophilic cells were notably in excess of the others.

Lewis mentions a slightly smaller brain in his dementia praecox subjects (average weight in 95 cases 1,270 gm.). He again

stresses the presence of small blood vessels in both the brain and the meninges, and is at pains to show that the perivascular spaces were "greatly dilated" and "doubtless were developmentally large," in contrast to appearances noted in other physical and mental diseases. The rather poor pictures in the monograph, however, are fairly unconvincing.

As succeeding reports on the pathology of schizophrenia tend to become more critical, one might pause at this juncture, albeit arbitrarily, and take stock of the ground covered in the selected publications from 1913-1923 that have just been reviewed. It becomes at once apparent that from the point of view of histopathology it was a rather productive decade, though it might not have been a very discerning one. Three of the major systems of the body—the nervous, the cardiovascular, and the endocrine—had already been invoked in the search for an organic pathogenesis. Changes in the brain were naturally looked for most avidly, and, in the absence of adequate controls, "changes" were found. The neurons were alleged to bear the brunt of the attack from the "pathogen"; hence, they were made to swell or to shrink, to be loaded with lipids and pigment, or be encircled by glial cells and strands, and even urged to disappear. Fibrosis of endocrine glands, especially of the gonads, had been invoked, and, finally, a small heart and a diminished vascular bed were held responsible. It was indeed refreshing to hear at least two voices of caution and of criticism.

II

It might be worth considering in some detail the observations of Dunlap[15] on brains from carefully selected cases of schizophrenia, as this paper strikes the keynote for this second (arbitrarily formed) period of review. His criteria for selection of brains for histopathological study were (1) an indubitable diagnosis of schizophrenia, (2) a patient under 40 years of age at the time of death (to exclude senile changes), (3) death due to an acute process, preferably accident or suicide, and not from a wasting disease, and (4) the performance of autopsy immediately after death, if possible. Trying to fulfill these conditions, he could study only 8 of 31 brains he received.

Perhaps the single most important advance over the previous investigations was the study of five brains from control cases, and as he said: "It has been harder to find suitable control cases than to find suitable cases of dementia praecox." All the different neuropathological features stressed by previous workers are dealt with in these two groups of brain studies; in not one of them could any significant difference be found between schizophrenics and controls. Thus, abnormal staining of neurons, "sclerotic" nerve cells, pyknotic nuclei, and intraneuronal lipid accumulations were encountered to the same extent in the two groups. The important question of an actual loss of nerve cells was resolved by counting (from the sections and from photomicrographs) the number of neurons in exactly corresponding areas of control and schizophrenic brains; the numbers were almost identical in the two groups. Finally, in neither of the two groups was there any detectable increase in neuroglial nuclei or fibers at any place. Dunlap naturally concluded that his study had "not shown even a suspicion of a consistent organic brain disease as a basis for the psychosis" of schizophrenia.

Following upon this unequivocal pronouncement, it is interesting to read the very cautiously worded review by Spielmeyer[16] of the problems besetting the histopathologist in his study of schizophrenia. Spielmeyer concedes the presence of small, nerve-cell-free zones in the cerebral cortex, of fatty substances in glial cells and vessel walls, and of fresh necrobiotic linear areas throughout the brain in a variety of conditions, including the normal state, and declares that in many of his own cases there was no deviation from normal histology. Nevertheless, he maintains that in acute stages he finds active destructive phenomena in the nervous tissue with progressive and

regressive glial changes, and on the basis of this, and on the authority of earlier workers, e. g., Alzheimer,[2,3] he tries to reinstate dementia praecox on an organic basis but without a *specific* pathology.

It is no wonder, then, that at the end of a very thorough examination of clinicopathological evidence for the concept of schizophrenia as a specific disease entity, Conn[17] was unable to discern any correlation between the histological pictures and the clinical disorder. On the one hand, there was no uniformity as to what constitutes clinically a dementia praecox reaction, and, on the other, a variety of toxic and organic conditions seemed to exhibit histopathological findings reported as being specific for dementia praecox.

In 1925, Lewis[18] also reviewed the pathology of dementia praecox and reported some autopsy findings, but he reiterated his thesis of primary hypoplasia of the cardiovascular system. He stressed that this was not due to atrophy or malnutrition (as occurs perhaps in tuberculosis), but that "the true praecox has an inferior hypoplastic constitution without adequate compensatory possibilities . . . and tends to deteriorate with age."

Another proponent of this vascular theory of schizophrenia was Winkelman.[19] He stressed two types of tissue reaction: (1) a swelling of endothelial cells of small blood vessels, with consequent narrowing of the lumen leading to anoxemia, and (2) edema of the brain. However, one cannot consider these observations seriously, since they were confined to not more than five patients with schizophrenia, all of whom had died of an acute illness, such as typhoid, meningococcal meningitis, or food poisoning.

Again, stopping here to look back on the labors of this second decade in our review, the years 1924-1933 present some interesting features. First, thinking and theorizing seem to have predominated over work, but without opening up any fresh avenues of approach. This could, to a great extent, have been due to the very significant paper of Dunlap, strongly challenging, if not entirely refuting, the previous notions of a rigid histological basis for the clinical picture of schizophrenia. After this, and after the reviews by Spielmeyer and Conn, one is left with the slightly disconcerting feeling that dementia praecox may or may not have some microscopic alterations in the central nervous system as its substratum, but that, even if it shows such changes, there is nothing causal or specific about them.

III

The whole subject tends to appear in a somewhat different and clearer light when one peruses the three detailed clinicopathological case reports by Ferraro.[20,21] The clinical diagnosis of schizophrenia had been repeatedly assigned to all the three subjects; two were hebephrenic, one was catatonic. All of them presented a syndrome of progressive mental and emotional deterioration, commencing in the second decade of life and terminating in a few years, without ever giving rise to definite neurological signs. Histopathological examination revealed in all a picture of diffuse encephalopathy, with widespread cortical demyelination (especially in the hebephrenics) as the dominant feature. There was also some loss of nerve cells and neurofibrils, and considerable gliosis. Fat-laden compound granular corpuscles and some lymphocytes were conspicuous in the demyelinated zones and around blood vessels.

Ferraro's conclusions are best given in his own words, summing up the second paper: This additional case supports, in my opinion, the contention that a mental picture, though lacking clinically in features of the so-called organic type of reaction, may result from an outspoken organic process of the brain. It also points to the view that it is not safe to assume that in dementia praecox no organic disease can occasionally be found and that the recent trend to consider schizophrenia not as a disease entity but as a syndrome resulting from more than one etiologic factor is in harmony with the accumulating experience.

A rather pertinent counter to the above argument is provided by a report of two cases of organic psychoses simulating

dementia praecox.[22] The true diagnosis on both these patients became available only in the fifth decade of life, after they had been in mental institutions for several years, and long after they started to manifest the classic picture of schizophrenia. The Rorschach, the EEG, and, finally, a brain biopsy determined the diagnosis—"chronic progressive degenerative brain disease." At operation, a considerable degree of convolutional atrophy of the frontal lobes was demonstrated, and a final diagnosis of presenile encephalopathy was thought of. Is it possible that cases like those presented by Ferraro would have revealed a different histology and been assigned a different diagnosis if the patients had lived on beyond the acute phase of their illness?

Roizin et al.[23] concurred with Ferraro when they discovered a neuropathological picture of acute symmetrical demyelination in the brain of a 34-year-old woman who had died after manifesting a brief acute phase of the catatonic schizophrenic reaction. According to the authors, the clinicopathological correlation here merely serves "to illustrate that a demyelinating process acting as a somatogenic factor may precipitate, in certain cases, an acute mental syndrome which may or may not be associated with fleeting neurologic symptoms."

In a discursive, but critical, lecture, Wohlfahrt[24] had also analyzed the situation and given his opinion:

> Since in medicine we require positive and not negative results as proofs of our contention, so far as I believe, the results of anatomical investigations obtained up to now speak neither for nor against the organic nature of schizophrenia assumed by various parties.

Nevertheless, he then proceeds, through descriptions and photomicrographs of Nissl-stained sections of cerebral cortex, thalamus, basal ganglia, and cerebellum of normal and of schizophrenic brains, to point out that he failed to find any appreciable differences between the two groups.

A somewhat newer concept was introduced in the neuropathology of schizophrenia (and manic-depressive psychosis) by the observation of Elvidge and Reed[25] that a swelling of oligodendroglial cells, with or without pyknosis of their nuclei, was a conspicuous feature in the brain biopsy material obtained from these two types of cases. Mild hypertrophy of astrocytes was often found to accompany the oligodendroglial swelling. As this phenomenon was found to persist over a year, or even two years, in the same subject, it was felt to represent a chronic process; and, as it was most pronounced in the subcortical white matter, it was believed to be associated with disturbances in the associational and commissural fiber pathways. Finally, by analogy with other states in which swelling of oligodendroglia is known to occur, the authors assume that in psychotic states also there may be a causal toxic metabolic factor.

Harking back to Lewis' concept of a primary vascular smallness in schizophrenia was the interesting study by Olkon[26] on the structure of the capillaries in the finger webs of over 1,000 schizophrenic patients, as compared with those in an equal number of normal subjects. He found a reduction in capillary density among schizophrenics: a mean of about 23 capillaries/5 sq. mm., as against 45 in the normal subjects. While his normal population revealed a relative constancy in the size of the capillary (with a diameter of about 6μ), his schizophrenic group showed a very wide variation in size —from 3.8μ to 9.3μ. Furthermore, they also showed fewer normal comma-shaped and many more bizarre-shaped capillaries, with a significantly paler color index and an irregular rate of blood flow. Olkon concluded that schizophrenia is associated with a defect in the capillaries and that this defect is directly related to the severity of the disease. He felt that schizophrenia belonged to the category of vegetative and metabolic disorders.

In a similar vein was the investigation of Cotton and associates[27] on the vascular bed of the retina in mental disease. Their approach and method appear to be of prognostic, rather than of diagnostic, value. They found no correlation between habitus in the Kretschmerian sense and the capacity

of the retinal vascular bed, or any between this and schizophrenia (or manic-depressive psychosis). But there was a high degree of correlation between the clinical status of the patient and the capacity of this bed; those who did not improve or who deteriorated had a small retinal vascular bed, and vice versa, in a large percentage of cases.

In this context, passing mention might be made of the report in Russian literature [28] of the presence of a large percentage of circulatory anomalies encountered in the course of 200 autopsies on schizophrenics. Finally, Malamud and Boyd [29] reported a case of sudden "brain death" in a schizophrenic, in which the concomitant occurrence of vasomotor disturbances in the circulation of the periphery (as evidenced clinically) and of the brain (as seen post mortem) was said to signify constitutional vasomotor lability in schizophrenia. They described ischemic and hemorrhagic necrosis around areas of capillary stasis and hemorrhage in the cerebral cortex and the cerebellum, but indicated that sudden "brain death" occurs in other psychoses and in nonpsychotic conditions.

A new concept of the pathogenesis of schizophrenia that arose during this period was centered along the gastrointestinal system. While some workers (review by Peters [5]) had attributed over 40% of deaths among schizophrenics to enteritis, it was Gaupp [30] who advanced the notion of a primary liver disorder leading to a toxic psychosis. He reported central lobular fatty degeneration in about a dozen cases of catatonia and believed this to result from an acute toxemia of unknown origin. However, the high incidence of concurrent infectious disease in a large proportion of his cases seems to cast suspicion on his observation. Lingjaerde [31] reported an unaccountable combination of liver and adrenal pathology and thought it important in schizophrenia. He described four cases of fatal catatonia with histological abnormalities in both liver and the adrenal cortex.

Finally, the endocrine system also came up again for its share of scrutiny, in the work of Hemphill.[32] He confirmed Mott's observations by testicular biopsies on nonparanoid schizophrenic patients. He found testicular atrophy limited to the seminiferous tubules and speculated that what was at fault was perhaps a gonadotropic hormone from the anterior pituitary.

Looking back upon this third period of our review (1934 to 1945), one finds history repeating itself, possibly at a more sophisticated level, in the way the emphasis of the work has again been laid on nervous and vascular tissues. The severe but nonspecific neuropathological alterations reported in a few cases (Ferraro [20,21] and Roizin et al.[23]) bring out the complexity of the relation between structure and function in the central nervous system, without establishing any cause-effect association, and, judiciously, the authors desist from positing an organic basis for schizophrenia. The only reliable evidence of a positive nature in the field of anatomic changes stemmed from the well-controlled study on the capillary.[26] This gained some support from the observations on retinal vessels,[27] and together they seemed to substantiate Lewis' contention of a small cardiovascular system in schizophrenia. This is *not* tantamount to saying that there is a causal significance to these findings, as they might as well be a result of the attitudes and activities of the schizophrenic way of life.

Among the new ideas on the pathogenesis of schizophrenia that arose during this third period under review, much importance cannot be attached to the swelling of the oligodendroglia, since it could be a postmortem artifact, and one which has been observed in the normal brain as well (Meyer [33]). The notion of a diseased liver with consequent metabolic toxicity in the body (e. g., Gaupp [30]) could have been interesting if the study had not been so thoroughly vitiated by the selection of subjects ill with toxic and infectious diseases. As Meyer again concluded: "None of these anatomical changes has a convincing claim to be a substrate of the psychoses." Some of them,

like the liver change, are very probably secondary phenomena.

IV

The last period under review (1946-1957) reveals a significant amount of literature on all the four systems of the body incriminated so far in this survey of the histopathology of schizophrenia.

In the case of the nervous system, one further novel idea of pathogenesis was presented in a series of papers by Papez and his associates.[34] First, they claimed to have shown the presence of intracytoplasmic "inclusions" in the neurons in a large number of brain biopsy specimens from schizophrenics. These bodies have demonstrated "vital activities" under dark-phase microscopy; they have been called "pleomorphic organisms." In the drawings accompanying the papers, these bodies are shown as particles, 0.5μ to 1.5μ in diameter, lying in clusters beside a pale, "inflated" nucleus. The authors then postulate that these organisms constitute the "causal factor" behind the various neuronal and secondary glial changes which they describe. These changes consist of an increase and then a decrease in intranuclear deoxyribonucleic acid, pyknosis, swelling and rupture of the cytoplasm, "neurofibrillar damage," "gliosis," shown by sclerosing fibers around astroglia cells, and proliferation of oligoglia in the white matter and of mesoglia and microglia nuclei around the blood vessels. All these are said to be "metabolic disturbances."

The outstanding neuropathological study in schizophrenia in this decade appears to be that carried out by the various associates of O. Vogt and reported at the First International Congress of Neuropathology, in 1952. Braitenberg,[35] studying the frontal cortex of a few schizophrenic brains, found a decrease in the staining quality and the number of nerve cells per unit volume in the cingulate region. He postulated that "physicochemical alterations," leading to a slight increase in the dimensions of a portion of cerebral cortex, could be responsible for these apparent changes. On the other hand, Baumer's investigation[36] on the nucleus lateralis and nucleus medialis of the thalamus, through Nissl-stained sections of 14 schizophrenic and 30 normal brains, showed qualitative and quantitative alterations in the neurons to a variable degree, but in the schizophrenic brains only. The anteroventral thalamic nucleus in 18 schizophrenic brains[37] showed a diminution in the number and a fatty deposition leading to degeneration of a number of neurons, with frequent increase in glial cells also. Though the normal control brains did not show these changes, brains from cases of nonschizophrenic mental disorders did.

Hopf,[38] of the same group of workers, looked at the pallidum and striatum of 10 brains of catatonic schizophrenics and reported much more tigrolysis and increase of scattered lipofuscin than in normal brains or in brains of hebephrenic or paranoid patients. Atrophic cells were also seen in four of the catatonic patients. He concluded that these investigations "do not yet permit us to regard the changes observed as the primary substratum of catatonia" . . . but that "they may be regarded as the anatomical expression of the motor disturbances in catatonia." As, of late, perhaps even greater interest has centered around the hypothalamic region, which has been invoked in the etiology of schizophrenia; the hypothalamic nuclei (the tuber cinereum and corpus mammillare) of eight catatonic and two paranoid schizophrenic patients were examined by Wahren.[39] Nissl- and Feulgen-stained sections revealed neither any particular loss in nerve cells nor any glial or vascular changes that were not encountered in a certain number of old people or in patients with other nervous diseases. Wahren summed up by saying: "Our method has not led us to discover any changes entitling us to think that the hypothalamic regions play an important part in producing the symptoms of schizophrenia."

In view of the stress laid by many of the previously mentioned histopathologists on

the catatonic form of schizophrenia (as against the other varieties), it may not be irrelevant to make a brief reference to Scharenberg and Brown's account [40] of the neuropathology of catatonic states. In three cases with catatonia of 4 weeks', 5 years', and 20 years' duration, respectively, they found identical changes in the brain, comprising "extensive intravital necrosis" with profuse reaction of all the three forms of glial cells. The most conspicuous change was ameboid degeneration of astrogliocytes (Alzheimer's description), and the authors touch upon the differential diagnosis of this feature. Since it is known to occur in severe disorders of metabolism, such as uremia, diabetes mellitus, toxic conditions like ulcerative colitis, and infectious diseases, it indicates possibly a profound disturbance of metabolism in catatonic states also.

On the basis of experience with several more cases, Ferraro [41] reaffirmed his original conclusion that typical clinical cases of the schizophrenic syndrome are compatible with both the presence and the absence of anatomopathological changes in the brain. Even when they are present, he cautioned against the conclusion that schizophrenia is an organic disease, since other possibilities are more likely. The histopathological changes may be the expression (1) of a complicating secondary organic process, (2) of a primary organic brain disease which may precipitate a schizophrenic symptom complex, or (3) of a psychosomatic integration resulting from the play of emotions and conflicts on the autonomic nervous system, particularly the vasomotor mechanisms and blood vasculature.

Coming to problems of physiopathology and histopathology of the circulatory system, the thesis of Shattock [42] on the somatic manifestations of schizophrenia provides a quantity of material, as well as a comprehensive review. In line with Lewis' data on the heart are Shattock's observations at autopsy on 25 schizophrenics. The heart of catatonic subjects was always small, with a remarkably thin auricular wall, frequently of the consistency of tissue paper. The ventricular musculature was normal, or even slightly hypertrophied. Autopsy of patients with affective, senile, and organic psychoses did not show the same reduction in the size of the heart or in the degree of atrophy of the auricular musculature.

Similarly, retinal blood vessels of a large number of schizophrenics, as compared with the retinal vessels of affective psychosis and of normal medical students, revealed tenuous retinal arterial trees. The difference was very pronounced in restless young schizophrenics, who suffered from severe peripheral cyanosis and other vascular abnormalities, such as contraction of the main limb vessels. This appeared to confirm the observations of Cotton et al., though Shattock could not assign a prognostic value to the capacity of the retinal vascular bed.

Shattock's extensive study of cyanosis and vascular responses in over 500 psychotic subjects showed that at room temperature (62-65 F), cyanosis of the extremities was present in 43% of female and only 5% of male psychotics. Under the same conditions the average surface temperature of the hands and feet of 30 female schizophrenics was significantly lower than that of 30 male affective psychotics. Temporary relief of cyanosis was afforded by any measure which secured vasodilatation, i. e., heating the body, reflex and reactive hyperemia, and administration of a vasodilator drug, and also by blocking the nerves of the limb. These physiological observations appear logically related, on the one hand, to the angiospastic retinopathy and, on the other, to the smallness of the cardiovasculature as a whole, reported previously. According to Zeligs,[43] vasoconstriction resulting from fear or anxiety in patients who show a tendency to sympathetic overactivity is the main cause of the vascular narrowing, retinal vasoconstriction being merely a focal manifestation of a general vasospastic state involving the peripheral vessels.

Turning to the endocrine glands, the problem of testicular atrophy appears to have found a definitive resolution in the work of Blair and his associates.[44] Testic-

ular biopsies were performed on the entire population of the research ward at the Worcester State Hospital. This included 17 chronic and 10 acute cases of "unanimously diagnosed" schizophrenia, all the patients being under 40 and free of organic disease. The combined group included all types of schizophrenia. Unequivocal results are reported: 1. Except for slight focal inflammation in two cases, there was not a single biopsy that could be regarded as showing anything pathological. 2. Without exception, all specimens had tubules, tunica propria, and Leydig cells within normal limits. 3. Mature spermatozoa were found uniformly, and (except in one case with inflammation) they appeared to be present in normal quantity. 4. In about a third of the cases there was an occasional sclerosed tubule or some thickening of the basement membrane; in no case did this exceed the frequency of such findings in entirely normal testes of the same age group. Regarding the somewhat contrary observations of previous workers, especially of Hemphill et al., the authors suggest that other factors, such as the wartime diet, genetic factors, or a higher incidence of mumps orchitis, might have altered their picture.

As against Blair's observations on male schizophrenics are Shattock's [42] on 30 female schizophrenics. Repeated smears of the vaginal mucous membrane from these subjects (and from 13 depressive and 13 normal subjects) between the ages of 25 and 40 showed that cornification of the vaginal epithelium was defective in many of the psychotics, especially in the schizophrenics. In two-thirds of the schizophrenics, the epithelial cells were much smaller than in normal subjects, and also rather rounded and markedly glycopenic. This picture was said to be identical with that of the "atrophic menopausal type" and to be a reflection of advanced ovarian dysfunction due to estrogen deficiency. The latter, in turn, was attributed to pituitary dysfunction. According to Shattock, deficient gonadotropic secretion is suggested by other signs of polyglandular disturbance, particularly of panhypopituitarism, such as an asthenic syndrome, among 5%-10% of catatonics, a lower basal metabolic rate in general (65% to 75% of the normal level), low systolic and pulse pressures, and "contracted" brachial, radial, and dorsalis pedis arteries in female schizophrenics with peripheral cyanosis, some hirsutism, and hyperpigmentation (also in females only), and a diminished metabolic response to ingested proteins.

Finally, a note may be made of two reports on the role of the alimentary system and the liver in schizophrenia. Thus, Buscaino [45] observed a small liver, changes in the small intestine, and activation and sclerosis of the splenic reticuloendothelial system and of the mesenteric lymph nodes. He felt that these findings were supported by physiological alterations, such as a reduced deaminating power of the liver, a diminished capacity for hippuric-acid synthesis (especially in catatonia), increased cholemia and bilirubinemia, urobilirubinuria, altered plasma albumin-globulin ratio, and a poor performance at other liver function tests. Buscaino made several assumptions: 1. He felt that the low weight of the liver in schizophrenics (cf. Lewis) and the changes he observed in the healthy parents of schizophrenics demonstrated that the affection is at least partly constitutional. 2. He then believed that the efficacy of "liver-protecting" treatment provides evidence in favor of the existence of hepatoenteric toxins in schizophrenics. 3. He thought these were toxic amines, which then acted on a predisposed nervous system to produce disseminated lesions in the cortex, white substance, and basal ganglia, and which were said to be responsible for the varied symptomatology.

Scheidegger,[46] in a "brief critical note," observed that changes in the liver in schizophrenia consist of vacuolation, pyknosis, and karyorrhexis of liver cells, variation in the size of these cells, and the presence of non-iron-containing pigment in both epithelial and reticulum cells. He found similar changes in persons of the same age group

dying of pneumonia and kidney and heart disease. He concluded that these toxic changes were not typical of schizophrenia and did not confirm the idea of a histopathological substratum in the liver typical of that disease. He compared the changes in the liver to those in the brain, and stressed the rarity of true reactive changes, scar formation, and gliosis, respectively, in these two tissues.

Looking back even on the few selected articles on the subject that have been presented in this fourth period of our review (1946-1957), it becomes apparent that correct appraisal is not always easy. In the field of neuropathology, one might first allude to the work of Papez et al. and of the associates of Vogt. Regarding the notion of micro-organisms in the brain causing schizophrenia, the idea being totally unconfirmed, one is forced to take cover under the remark of a previous reviewer [47] that this concept "defies critical evaluation at the present time." Needless to say, none of the clinical types of schizophrenia has ever been known to manifest a picture like that of an infectious disease. The negative findings reported by the Vogt school of workers for different areas of the brain are quite significant, especially Wahren's report on the controversial region of the hypothalamus. No more importance can be attached today than before to the occasional occurrence of scattered neurons showing tigrolysis, increase in lipofuscin, or "atrophy," or even to the loss of cells in parts. Perhaps an attempt at *quantitative* comparison between schizophrenic and normal brains, such as that undertaken by Dunlap, might have induced some of these workers to modify even their few statements on the presence of lesions in schizophrenia.

From Alzheimer to Hopf, through Gurd, Malamud, Ferraro, Roizin, and Scharenberg, the one fairly consistent thread of evidence presenting the histological correlate of a clinical picture appears to be in catatonic schizophrenia, particularly of the acute variety. Even here, however, two mitigating factors are worth noting. First, the pathological picture described has varied all the way from mere neuronal changes, to proliferation of Alzheimer's ameboid glia, to demyelinating encephalopathy, to extensive necrosis and gliosis. Second, these changes might be related merely to the phenomenon of catatonia, irrespective of the total clinical (neurological *and* psychological) picture of this type of schizophrenia.

Peters,[5] presenting his own work on the brains of 8 executed criminals and 14 schizophrenic subjects of different types, apparently failed to be impressed by any histological difference between these two groups, finding cellular outfall, "sclerosis" of neurons, "haziness" of cytoplasm, and lipid accumulation in both.

Perhaps a little more attention is merited by the anatomical differences (not changes) noted by various workers in the cardiovascular system. Shattock's well-controlled and well-documented physiological and histological observations on the smallness of the heart and blood vessels bring to the fore again the ideas of Lewis and Olkon on a primary defect in this system in schizophrenia. But even granting this, do we get any closer to understanding the pathogenesis of this disorder? An over-all reduction in the quantity of cerebral vasculature could then lead one to expect a diminution in the blood flow and oxygen consumption of the brain, but the critical work of Kety and his associates [48] does not bear this out at all. Nonetheless, the probability of a small heart in schizophrenia appears to be getting well established, as further indicated by the diminished force of contraction of the heart recorded by the ballistocardiograph. Cardon [49] found the mean amplitude of the I-J complex in 11 male schizophrenics to be 8.55 mm., the corresponding figure for normal men of equivalent body weight being 11.77 mm. ($P<0.01$). He did not find any significant difference in the blood pressure between the two groups. It is not impossible that these deficiencies of the circulatory system in schizophrenics may bear no etiological connection to their mental derange-

ment, or they may be the reflection of their altered tempo of living.

In the field of endocrinology, from the histological point of view, there does not appear to be much literature available. Mott's [7] and Hemphill's [32] finding of severe fibrosis of the testis has been finally denied and refuted by the critical work of Blair et al.[44] Lewis' original observation [14] of atrophic degeneration of the parenchymal elements of most endocrine glands, including the anterior pituitary, does not appear to have found either refutation or confirmation from histopathologists. Clinical and physiological evidence (which it is not the purpose of this review to examine in detail) has at times suggested some panhypopituitarism in schizophrenic (especially female) patients, as Shattock [42] has tried to show. Even granting this, and notwithstanding her observation of defective cornification and glycopenia of the vaginal epithelium of two-thirds of her subjects, one would have to hesitate before attributing a pathogenetic role to the pituitary, or to any other endocrine gland—among other things, changes consequent to poor nutrition, institutionalization, and states of anxiety would have to be considered.

The liver also seems to stand in an analogous situation: apart from a lot of assumptions and uncontrolled observations, we are left, in schizophrenia, with an organ that is probably smaller than normal (Lewis [14] and Buscaino [45]), but which otherwise shows no more histological alterations than normal livers or the liver in cases of extrahepatic organic disorders (Gaupp [30] and Scheidegger [46]). Once again, tests from the repertoire of clinical pathology are applied and a few deviations from the norm taken to indicate that the liver is so diseased that toxic products ("amines" preferred!) accumulate and damage the nervous system, and this so specifically as to produce schizophrenia. Peters,[5] in his exhaustive review of the German literature, mentions a number of workers who considered gastrointestinal lesions to be the most significant histological change in schizophrenia. According to some, enterocolitis was the cause of death in 40% or more! For instance, Reiter [50] reported hyperemia and round-cell infiltration in the pyloric region, as also in the large and small bowel and in the mesenteric lymph nodes in almost all of 23 autopsies on schizophrenics. It is interesting, and almost humorous, to note that Witte [51] quickly repudiated the above observation by finding similar changes in 20 out of 22 control cases! He found only 10% of a series of 1,200 mental asylum patients to have died of gastrointestinal disease.

Summary

Looking back, then, on this total, though sketchily presented, historical picture of the histopathology of schizophrenia, the conclusion seems inescapable that no specific change in any tissue or system of the body has been demonstrated that can account for the clinical syndrome of schizophrenia. Even nonspecific histological changes appear to be rarely found, and, when detected, to be unrelated to the psychological derangement. The vast body of literature on the subject falls into two categories: positive pronouncements of anatomical alterations believed to be responsible for the pathogenesis of schizophrenia, and negative reports demolishing this claim. As noted in each of the four successive periods of this review, the great majority of well-controlled and critical studies fall in the latter category. As far as was possible, the reports selected to represent the two categories in any of the four periods have been allowed to speak for themselves, often in the original author's words; this apposition of one type of work or of one sort of conclusion against another has usually made criticism self-evident, and has absolved the reviewer from the necessity of commenting on each paper separately.

At the end of the longest, most recent review of the subject, the author (Peters [5]) lamented: "The result of this communication is unsatisfactory. The basic pathology in schizophrenia, as in idiopathic epilepsy, is not clear." It is pertinent that Peters

does not restrict his remark to histopathology; in the term "basic pathology" he probably includes physiological pathology and metabolism as well, implying that the pathogenesis of schizophrenia is not clear. Whether agreeing or disagreeing with this generalization, and without attempting to review all aspects of the currently popular and already extensive subject of biochemistry and metabolism in schizophrenia, the research worker of today might profitably take stock of his specific field of interest and make sure that thoughts and theories are not passing for facts and things.

At the risk of sounding pessimistic, it appears to me that it is the lesson of the past that history repeats itself. One need not be shocked, therefore, if the current notion of there being a distorted molecule behind a distorted thought is as difficult to demonstrate as the older belief of a defective neuron behind a defective thought.

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Use of Lysergic Acid Diethylamide in a Psychotherapeutic Setting

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In experimental psychiatry the hallucinogenic drugs have a firmly established position; hundreds of articles attest to the growing interest in their psychotomimetic activity. As an adjunct to psychotherapy, however, their potential has been incompletely investigated.

The initial mention of lysergic acid diethylamide (LSD-25) in this connection appears to be the 1950 publication by Busch and Johnson,[3] where the drug was described as having "profoundly influenced the course" of progress of eight cases of psychoneurosis. The remembering and reliving of early traumatic episodes were especially noted.

Of subsequent researchers, Abramson[1] has investigated the drug most extensively in this country. He uses LSD-25 in conjunction with analytic treatment. Patients are given small doses periodically when they appear to be at a standstill in therapy. He noted that LSD-25 is characterized by pharmacologic safety, maintenance of the patient in a conscious and cooperative state, and repetition without evidence of addiction.

Frederking[7] uses small doses both of mescaline and of LSD-25 in his office practice. He speaks of a dream-like state which occurs and can be analyzed, with a resulting psychocatharsis.

Sandison and his colleagues, in England, have evolved a special inpatient technique whereby a ward of Powick Hospital is reserved for LSD patients. Treatments are given weekly. Dosages increase from 25μg. to levels of 100μg. or 200μg. The patient-treatment team consists of a psychiatrist in charge, nurses who are in attendance during drug sessions, and the therapists, who conduct group therapy apart from the drug experiences.

Their recent report[11] on 94 patients includes follow-up periods as long as five years, and their 65% improvement rate is impressive in view of the fact that their patients had chronic, severe neuroses which had proved resistant to all other types of therapy. The authors stress the fact that all their cases were "in danger of becoming permanent mental invalids, lifelong neurotics or suicides."

Work by others in the field[2,5,6,8-10,12,13] seems to indicate that LSD-25 lowers resistance and facilitates the appearance of unconscious material, which can then be dealt with therapeutically. The investigators also mention the heightened relationship between patient and doctor and note that drug action does not interfere with clarity of consciousness; in fact, recall of past events is heightened.

In an earlier study at the Brentwood Neuropsychiatric Hospital, in which psychological test changes in normal volunteers were studied,[4] there were further indications of the possible therapeutic value of LSD-25. Although individual reactions varied over a wide spectrum, there was,

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in general, a lowering of ego defenses, an intensification of the interpersonal relationship during the session, and an outpouring of unconscious material. Some of the subjects described their experiences as psychotic, but others reported unusually pleasant and insightful sessions. A few believed that their experimental exposure to the drug had a sustained beneficial effect on subsequent behavior.

The present study was a preliminary exploration of LSD-25 as an aid to the uncovering and acceptance of unconscious material and to determine whether the therapeutic process could be accelerated. A total of 29 patients whose diagnoses varied from depressive states to borderline schizophrenia were treated. There were also a number with character disorders, and one schizophrenic. This report is concerned with 22 of these patients, ranging in age from 21 to 60 years, who have had a follow-up period varying from 6 to 17 months. The seven not to be reported have had follow-up periods of less than six months.

Method

Weekly or biweekly treatments were given; because of the rapid onset of tolerance, sessions were never less than three days apart. Initial doses were one 25μg. tablet; subsequent interviews were conducted by increasing the dose by increments of 25μg. until a level of 100μg. or 150μg. was reached. Two patients, resistant to the drug, received 50μg. increments. On five occasions 500μg. of ALD-52 or MLD-41,* amounts which appear to be equivalent to approximately 250μg. of LSD-25, were administered.

The gradual increase in dosage minimized unpleasant side-effects. Anxiety was usually absent or negligible, and as the patient progressed to the higher dosage levels, deeper areas of the unconscious seemed to become available.

The number of drug treatments ranged from 1 to 16, with a mean of 4.6. When a patient required more than four sessions, it was found that optimal therapeutic progress was made if longer periods elapsed after treatments in which a good deal of significant material was uncovered. Contact with the therapist was maintained by telephone or interview, and therapeutic gains appeared to be integrated and consolidated when the patient was allowed to listen to the tape recordings of particularly insightful sessions.

Drug activity could be noted usually for four hours at low doses and from six to eight hours when more than 75μg. was prescribed. The patient was on a couch during this time in a pleasant room, with the therapist constantly in attendance. Food was served when the patient became hungry. Music was played initially to aid in relaxation and was incorporated into the treatment after repeated observation that certain selections seemed to potentiate the drug action.

In addition to the music, other aids were found helpful. A mirror was available, and frequently the patient was able to project his unconscious concept of himself into the reflection and to deal with it objectively. Family photographs, especially of spouse, parents, and siblings, enabled the subject to externalize associated conflicts. Toward the end of each session, the patient was taken to the hospital art clinic to draw or paint whatever he desired. This seemed to augment the therapeutic process and to provide an opportunity to objectify subjective experiences.

The relationship between therapist and patient is of crucial importance during LSD-25 therapy. Almost every investigator has emphasized the enhancement of transference which occurs. It was observed in this series to be generally of a positive nature; however, on the few occasions where negative transference occurred, along with especially disturbing unconscious material, a straightforward examination of

* These compounds are acetyl and methyl analogues, respectively, of lysergic acid diethylamide.

these feelings helped with the resolution of the problem. The discussion of the feelings of the patient toward the therapist is not to be construed as an analysis of transference in the orthodox sense.

A patient often reexperienced repressed events with such vividness and force that they were described as having been "relived"; at the same time, he could witness these incidents with some detachment. Occasionally, the patient could recognize his problems even when they appeared in symbolic form. More frequently it was necessary to interpret the unconscious material as it arose. Such interpretations, which in conventional psychotherapy might have had devastating effects, appeared to be accepted without difficulty. An important aspect of the therapy was to direct the patient toward the frightening or painful symbolic material; if he was able to do this, its fearful or painful character seemed to dissolve.

The therapeutic approach was of the more direct, intuitive type used with schizophrenic patients. It is understandable that a directive, personally involved therapy, which is applicable to psychotics, may be appropriate, since the LSD-25 state also involves dissolution of the ego, hallucinatory imagery, depersonalization, and other schizophreniform characteristics. Because of the unusual and extremely subjective nature of the experience, the therapist should have had personal experience with the effects of LSD-25.

During intensive abreactions or at those times when ego disintegration was experienced as a psychotic-like state, it was helpful to have both a male and a female therapist present. They also served as surrogates for inconsistent, manipulating, or rejecting parents and often became a focal point for the projection of intense affectual discharge.

When critical problems were uncovered, various degrees of anxiety and somatic distress were felt. The discomfort disappeared when its psychogenesis was understood by the patient. Sometimes psychotic-like episodes or "death" in various terrifying, overwhelming, or excruciatingly painful ways was experienced. The patient was always encouraged to surrender completely to whatever was to happen, and the word most commonly used by him after such an experience was that he felt "purged."

As the problems were worked through, the patient underwent what might be termed an integrative experience. This involved a massive reduction in self-conflict, the patient having accepted himself for what he was, and, finally, a feeling of harmony with his environment. It is felt that this had therapeutic significance.

It is important that the insights achieved during drug sessions be put into action. Continuing psychotherapy is valuable in restructuring of habit patterns once the drug series has initiated a change in viewpoint and motivation. From our observation it appears that optimal use of the drug may be with drug treatments set within the framework of conventional psychotherapy.

Results

Of the 22 patients in our series with a follow-up period of at least six months, 16, or slightly over 70%, are improved. The difficulties in assessing improvement following psychotherapy are not limited to this study. The agreement of the two doctors, the patient, and the person closest to him, plus objective evidence of a better situational adjustment, were necessary before he was considered improved.

Improvement with LSD-25 therapy does not appear to be restricted to patients in any one diagnostic category. Patients whose neuroticism was manifested by chronic anxiety or compulsiveness did well. Four with depressive states, one of them with a history of severe periodic depressions, persisting through seven years of analysis, improved. Four patients with passive-aggressive character disorders also showed favorable changes. Three others who improved were one with borderline schizophrenia and two with immature, hysterical personalities.

A type apparently not conducive to good results is the inadequate, schizoid personality. Two of the unimproved were in this category; one had 16 sessions; the second did not complete treatment. A third unimproved subject was a hospital patient with a diagnosis of schizophrenia who may actually have had a severe character disorder. The other three therapeutic failures showed substantial initial improvement, which was not sustained or consolidated by alteration in behavioral patterns. All three felt much better for from one to four months, and then relapsed.

The most favorable prognostic factor is the patient's genuine desire to get well. Ego strength and intelligence are important, but motivating drive is primary, and it must be more than just looking for the magic of an easy way out. Frequently the more troubled the patient the better the outlook, since impetus to change may be greater.

Although the follow-up period of from 6 to 17 months is not sufficient to establish long-term effects, these preliminary impressions are encouraging. The improved group appears to be separating into two subgroups. The larger group consists of patients who, on the whole, are maintaining their gains. They have contacted us from time to time for help with a current problem.

The second group is smaller but more impressive. They have shown no evidence that additional therapy is necessary and have continued to move toward emotional maturity on their own.

Potential Dangers

The dangers associated with the use of lysergic acid relate to its psychological, not pharmacological, activity. Suicide appears to be a definite hazard. Stoll [14] speaks of two suicides in Europe following exposure to LSD-25. One of these subjects had been given the drug without her knowledge. Savage [12] had a schizophrenic patient who committed suicide after treatment with the drug.

We have observed transient depressions occurring during the evening after an LSD-25 experience which may have been due to one of several factors: (1) an inability to incorporate unacceptable traumatic material uncovered during an interview; (2) a feeling of being overwhelmed by the effort necessary to repattern one's life; (3) "coming back to earth" after a transcendent experience. We have insisted that an understanding person stay with the patient during this period. A more prolonged depression may develop when the insights acquired are not translated into the life situation. Continuing therapy is recommended here.

A complication that might be anticipated is the precipitation of a prolonged psychosis with LSD-25. This was not encountered in this series, nor have we found such an event in the literature. However, one case was indirectly observed in a patient with a compulsive personality who had previously had five years of analysis. He was given two LSD-25 treatments of 50μg. and 100μg. Although the patient is functioning extremely well in his job and life situation, systematized delusions in the religious area and surrounding the drug are present.

None of our patients required termination with chlorpromazine because of intolerable affectual discharge. There was also no indication of psychological addiction. The rapid onset of tolerance makes physiological addiction unlikely.

Several investigators mention the possibility of momentary LSD-like states for periods of as long as a year after treatment. We have also observed the appearance of such after-effects. This appears to be due to a facilitation of access to the unconscious which need not be anxiety-provoking if the patient has been informed of its significance.

A further precaution that must be taken arises from the impairment of motor coordination seen in connection with full dosages of LSD-25. Patients should not attempt to drive a car until the drug effects have worn off.

Summary

Lysergic acid is an interesting, and a possibly important, aid in the psychotherapeutic process. The patient-therapist transaction is intensified, permitting more penetrating interpretations and a more direct approach to the basic problems. Repressed memories can be recovered, and the symbolic projection of unconscious conflicts is vivid and affect-laden. Abreaction of underlying problems insightfully may be followed by an experience of integration, in which the patient accepts himself for what he is and sees himself in harmony with his environment.

Short-term results in nonpsychotic patients following a brief course of LSD-25 interviews are encouraging. Complications were not encountered, although potential dangers do exist. Further investigation of patient selection, mode of action, and technique are necessary.

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An Effect of Exercise, Skin Shock, and Ascorbic Acid on Serum Oxidase Activity

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In 1957 Akerfeldt [1] reported that when the N,N-dimethyl form of *p*-phenylenediamine (PPD) is added to serum the PPD becomes oxidized to a red-colored substance. He found that serum from schizophrenic patients oxidized PPD at a faster rate than serum from normal controls. A rapid rate of oxidation was also found in a large percentage of patients with liver disease, neoplasm, and pregnancy in the last trimester.[2]

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In this reaction a 0.1% solution of N,N-dimethyl-*p*-phenylenediamine is added to an equal quantity of serum. The increase in optical density is then measured spectrophotometrically for six minutes at wavelength 552 mμ. A time curve is then derived which is believed to be the resultant of a number of factors in serum,[3] among which are ascorbic acid concentration, ceruloplasmin activity, and certain sulfhydryl compounds. (A typical curve is shown in Figure 1.) The lag period before the initial rise is believed to be due to the influence of ascorbic acid, and it increases in length

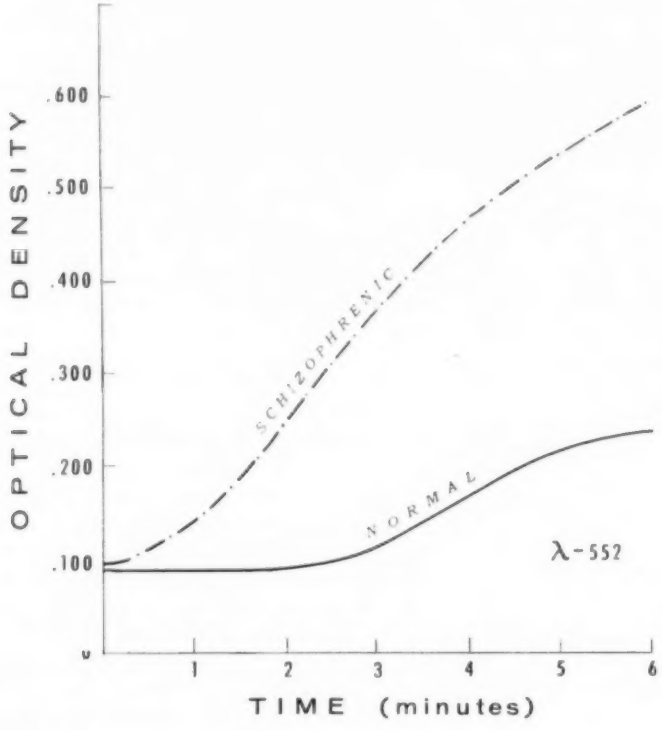

Fig. 1.—Typical curves obtained from the oxidation of N,N-dimethyl-*p*-phenylenediamine (PPD) by normal and schizophrenic serum.

as the ascorbic acid concentration increases. The slope of the curve rises with increasing enzymatic oxidation of PPD by ceruloplasmin, but is probably affected by many other substances found in the serum, including glutathione.

In an attempt to repeat Akerfeldt's results, we performed this procedure with the serum of 47 normal controls, 81 schizophrenic patients, and 11 patients with involutional and psychotic depressive reactions. In our procedure, all subjects were fasted for 12 to 15 hours prior to the withdrawal of blood. Samples were read on a Coleman spectrophotometer at 60-second intervals against a blank of each subject's serum. Oxidative activity is reported in terms of the increase in optical density at the end of six minutes of oxidation of PPD.

We found that the mean increase in oxidative activity over a time period of six minutes was 0.284 for the schizophrenic patients, 0.267 for the involutional and psychotic depressive reactions, and 0.211 for the normal group. The results of both the depressed group and the schizophrenic group are significantly different from the result for the normal group at the 0.01 level. Table 1, which is a comparison of results for the normal group and for the schizophrenic group, demonstrates that there is considerable overlapping in the results. However, 23% of the schizophrenic patients had results which were higher than any values found in the normal controls.

Effects of Ascorbic Acid

As a result of this finding, we became interested in exploring some of the factors that might affect oxidative activity in serum. Inasmuch as ascorbic acid was known to inhibit the reaction and to produce lower results as its concentration increased, it was possible that low concentrations of ascorbic acid might, conversely, produce elevated serum activity. In order to study the effects of ascorbic acid on serum, we first added varying concentrations of this substance, in vitro, to the serum of both schizophrenic and normal subjects.

Figure 2 demonstrates the effects of 13μg. of ascorbic acid per cubic centimeter of serum. It will be noted that the lag period is increased by five minutes for this particular serum. If the curves are followed after the lag period ends, their slopes are found to be parallel. This would indicate that, in vitro, the ascorbic acid affects mainly the lag period and not the slope of the curve.[1]

We then became interested in whether ingested ascorbic acid could reduplicate this effect on the serum. Among the subjects tested with ascorbic acid was a pair of 11-year-old identical twins with schizophrenia. Curves representing this test prior to treatment are demonstrated in Figure 3.

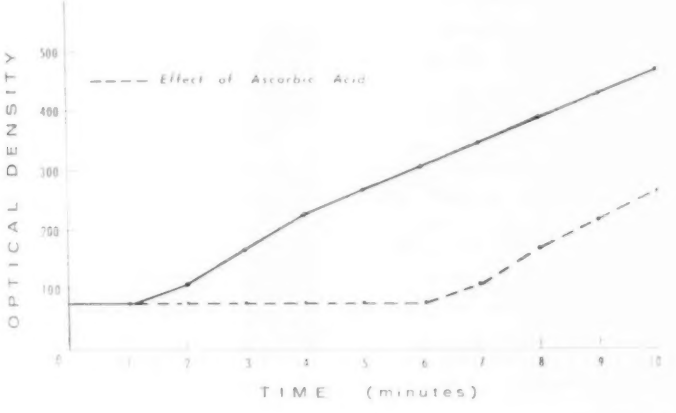

Fig. 2.—Effect of 13μg. of ascorbic acid (added in vitro) on the oxidation of PPD by serum.

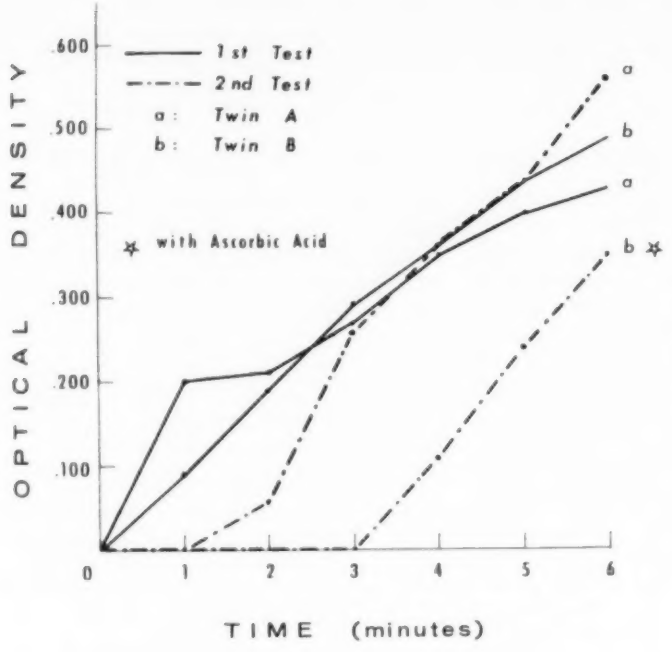

Fig. 3.—First test: oxidation of PPD by serum of schizophrenic twins. Second test: oxidation of PPD by serum of same twins after treatment of Twin B with 150 mg. of ascorbic acid t. i. d. for one week.

One of the twins was then given ascorbic acid, 150 mg., t. i. d., for one week, while the other twin was not given any supplementary ascorbic acid. At the end of the week, serum from the twin who received ascorbic acid demonstrated a marked increase in lag period, without an appreciable change in slope after the lag period. The nontreated twin also showed a slight increase in lag period, possibly as a result of improved diet in the hospital.

These studies demonstrate that ascorbic acid, in vitro or in vivo, has a profound effect on the results of this procedure. However, direct determinations of ascorbic acid in serum[5] demonstrate that low concentrations of ascorbic acid alone cannot account for the elevated oxidative activity found in the serum of some patients. While some patients with increased oxidative activity do have low ascorbic acid levels, which might be dietary in origin, we have found patients' sera with normal levels of ascorbic acid which oxidize PPD at a higher rate than any normal serum. Also, while ascorbic acid affects primarily the lag period, certain patients demonstrate a marked increase in slope.

Effects of Rest and Exercise

On one occasion, one of our controls who is a hospital attendant became actively involved in restraining a patient immediately after we had taken a sample of his blood for the procedure. A second sample, taken shortly after his struggle with the patient, was found to be markedly different from that taken before the exertion. This led us to investigate the effects of activity and rest on the results of the procedure.

In our method, serial blood samples were taken at similar intervals from each of six schizophrenic patients and six normal controls who rested for 60 minutes after the first sample, and from another group of six schizophrenic patients and six controls who performed an exercise test after the first sample. Groups were closely matched for age and sex. Different groups were used to obtain data on resting and exercise, since

TABLE 1.—*Distribution of Results of Oxidation of PPD* by Serum*

Optical Density †	Normal Group		Schizophrenic Group	
	No.	Per Cent	No.	Per Cent
Below 100	5	11	6	7
100-149	5	11	7	9
150-199	9	19	10	12
200-249	8	17	13	16
250-299	12	25	9	11
300-349	6	13	12	15
350-399	2	4	6	7
400-449	0	0	7	9
450-499	0	0	4	5
500-549	0	0	3	4
Over 550	0	0	4	5
No. of subjects	47	100	81	100
Mean optical density after 6 min.	211		284	

* N,N-dimethyl-*p*-phenylenediamine.
† Times 10^{-4}.

it was not desired to do as many as 14 venipunctures on any one subject. All bloods were refrigerated immediately after drawing, and all laboratory procedures were begun within two hours.

Figure 4 is a comparison of the effect of 60 minutes' rest on a group of six patients with relatively high initial serum oxidative activity (mean 0.293) and six normal controls with an initial mean oxidative activity of 0.215. After resting both the patients and the controls by having them sit quietly for 60 minutes, the mean oxidative activity of the patients fell to 0.225, while that for the controls remained essentially the same. Thus, prior to resting, the patient group had high oxidative activity. However, if both patients and controls were rested for one hour, the results for the patient group were essentially the same as those for the normal control group.

It is not known why rest causes a drop in the oxidative activity of patients' sera without significantly changing the sera of normal controls. It is possible that the patients were more active than the controls while on the ward prior to the test. This explanation, however, is not consistent with our observations, since, in the main, quiet patients were selected for the procedure. Another possibility is that the drop in the level of the normal controls' sera occurred during the few minutes' rest while they were waiting for their first blood to be drawn, whereas the drop in the level of the patients' oxidative rate did not occur until after further rest.

Table 2 shows the effect of a standard exercise test, which consists of jumping up and down 150 times, after which most subjects were breathless and fatigued. Serum was obtained from each subject immediately prior to exercise and at intervals of 5, 10, 15, 30, and 60 minutes following the exercise. For this procedure a group of six

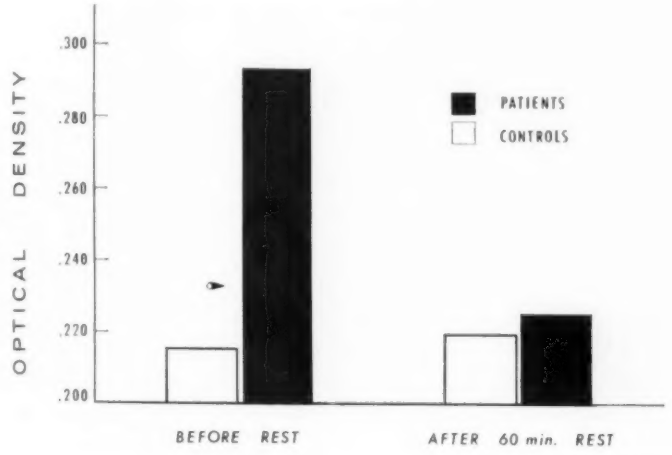

Fig. 4.—Effect of 60 minutes' rest on the oxidation of PPD by serum from six normal controls and six schizophrenic patients.

TABLE 2.—*Increase in Oxidation of PPD* by Serum from Schizophrenic Patients and Controls After Performance of Standard Exercise Test*

Patient No.	Optical Density † Before Exercise	Maximum Increase in Optical Density After Exercise	Length of Time for Maximum Increase, Min.
	Controls		
1	15	70	30
2	295	15	15
3	240	100	5
4	310	100	5
5	130	35	5
6	250	30	5
Means	207	58	
	Patients		
1	255	115	5
2	25	245	15
3	310	55	5
4	330	90	10
5	75	140	10
6	135	5	60
Means	188	108	

* N,N-dimethyl-*p*-phenylenediamine.
† Times 10^{-3}.

schizophrenic patients with a low mean oxidative rate (0.188) was obtained and compared with a group of six controls with a mean oxidative rate, again, close to that of our larger control group (0.211). The distribution of oxidative rates within the patient group was similar to that of the control group prior to exercise.

It was found that both patients and normals showed an increase in oxidative rate after exercise. When the increases in the two groups are considered together, the increase is significant at the 0.02 level. While there is considerable variability within both of these groups, and the groups are too small to make a comparison of one with the other, it is nonetheless interesting that the mean increase in the patient group was more than twice the mean increase of the control group. This increase was in the slope without a change in lag period, indicating that this represents a change of levels not of ascorbic acid but of some other, unknown factor.

From these data it is clear that rest and exercise can have a significant effect on the results obtained from the oxidation of PPD. When the control group had just been engaged in vigorous activity and the patient group had been resting for one hour, our data indicate that the controls would then have higher values than the patients. Therefore, it is clear that rigid control of physical activity must be maintained to give comparable results on this test.

While these data do not demonstrate an abnormal response in oxidative rate in either exercise or rest in schizophrenic patients, they none the less suggest that further investigation of the effect of exercise and rest should be carried out. Considerable individual variability in rate and duration of response to exercise was noted. However, these differences can be interpreted only after rigid controls of activity are maintained for several hours prior to the initiation of the exercise test.

Effects of an Electric Shock

In order further to clarify factors that may be involved in elevated serum oxidative activity, we measured the effect of an emotionally stressful situation by subjecting patients and normals to a skin shock on the hand. Determinations were made on serial blood samples taken before and after the shock. No significant change was observed in either the patient or the control group. On the other hand, considerable change was noted after electroshock treatment in 12 patients who were premedicated with succinylcholine and thiamylal to minimize muscular activity (Fig. 5). The oxidative rate was found to increase markedly, reaching a maximum 15 minutes after shock treatment and returning to preshock levels within 30 minutes after treatment. At present we have not eliminated the possibility that the effects attributed to EST may be the result of the premedication used.

Comment

It is evident that the rate of oxidation of N,N-dimethyl-*p*-phenylenediamine dihydro-

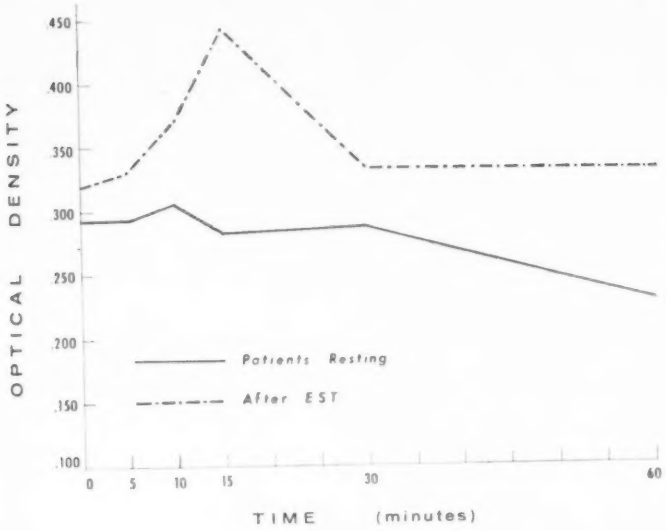

Fig. 5.—Effect of electroshock therapy on oxidation of PPD by serum. Controls are a separate group of untreated patients.

chloride by serum is influenced by many factors. Changes in monovalent anions, such as nitrate, chloride, bromide, formate, and acetate ions, accelerate this process in low concentrations, but in high concentrations show an inhibitory effect. Both the acceleration and the inhibition effects increase with decreasing pH.[6] As a matter of interest, we have been able to obtain a considerable rise of oxidative activity of serum simply by ingestion of sardines.

Although 23% of our schizophrenic patients exhibited oxidation rates higher than any of the normals, Akerfeldt's procedure appears to be an unreliable test for diagnostic purposes because of the interaction of so many variables. However, if properly controlled by means of serial samples taken at intervals after standard stress, such as exercise or electroshock treatment, this procedure might provide a useful measure of individual responsiveness to stress.

Summary

Serum from 47 normal controls, 81 schizophrenic patients, and 11 involutional and psychotic depressive patients was evaluated for its ability to oxidize N,N-dimethyl *p*-phenylenediamine dihydrochloride.

The patient groups had significantly higher levels than the normal controls, although there is considerable overlapping.

The results of this procedure are affected by ascorbic acid in vitro and in vivo.

Higher values in schizophrenic patients may be related to increased activity prior to the test, or to an abnormal response to exercise and rest.

Skin shock did not affect oxidative activity, while EST did.

Serial determinations on serum drawn after a standard physical stress might provide a useful measure of responsiveness under properly controlled conditions.

Mrs. Muriel Henderson gave technical assistance in the preparation of this article.

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Relative Effectiveness of Various Components of Electroconvulsive Therapy

An Experimental Study

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Electroconvulsive therapy is a complex treatment which involves at least three factors: (1) introduction of a quantity of electrical current into the brain; (2) rapidly induced loss of consciousness, and (3) motor convulsion. It is the aim of this study to determine experimentally the extent to which each of these components contributes to the therapeutic effectiveness of the over-all treatment. Although ECT is extensively used in the treatment of the mentally ill, it has never been firmly established whether it is the electrical current itself, or the motor convulsion, or the resulting unconsciousness which is the major therapeutic factor of the treatment; or whether the entire treatment complex is necessary.

The literature abounds in statistical and case reports comparing various forms of shock treatment, but few controlled studies have been done, especially with regard to the specific aim of this investigation (i. e., to determine the therapeutic efficacy of certain components of the treatment process). An outstanding exception is a recent study by Miller, Clancy, and Cumming,[1] which compared the results of comparable groups of chronic catatonic patients receiving ECT, or thiopental (Pentothal) sodium alone, or a combination of thiopental sodium and unidirectional-current nonconvulsive electrical stimulation. They found no significant differences among the three treatments in degree of "social improvement," although significant improvement (especially in terms of increased activity and interest in the environment) occurred with each treatment. Fink, Kahn, and Korin[2] compared grand mal convulsions with subconvulsive stimulation and concluded that ECT was a nonspecific traumatic induction of a state of altered cerebral function. These authors report in their abstract that they found the rating of improvement to depend on the pattern of interaction of the patient with the environment and the expectations of the evaluators.

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Wilfred J. Dixon, Ph.D., served as statistical consultant for this study. The following members of the Veterans Administration Hospital staff aided in various aspects of this study: H. D. Strassman, M.D.; A. A. Unger, M.D.; J. T. Ferguson, M.D.; J. L. Haskins, M.D.; A. S. Nissen, M.D.; K. S. Ditman, M.D.; M. Schreiber, M.D.; W. B. Skrdla, M.D., and the resident and nursing staffs of the Acute Treatment Service.

Method

Subjects.—Subjects in the study were 97 male psychiatric patients in a Veterans Administration Hospital. Most of the patients suffered from chronic schizophrenic reactions, approximately one-fourth having no record of prior hospitalization. The length of time since the original onset of illness ranged from less than 1 month to over 10 years. Course of illness was marked by remissions and recurrences in 67 patients; 24 subjects had an unremitting course of illness with prior hospitalization, and 6 had become ill recently for the first time. The average age was 35, with a range of 18

TABLE 1.—*Composition of the Treatment Groups with Respect to Diagnosis*

Diagnosis	Treatment Group					
	Regular ECT	ECT & Anectine	ECT & Thiopental	Thiopental	Nitrous Oxide	Total
Schizophrenic reactions	11	10	17	15	14	67
Catatonic type	3	1	4	3	3	14
Hebephrenic type	—	—	1	—	1	2
Paranoid type	6	9	7	7	6	35
Chronic undiff. type	2	—	5	5	4	16
Depressive reactions	8	10	3	5	4	30
Schizoaffective type	6	4	2	2	—	14
Psychotic depression	1	3	—	1	2	7
Involutional depression	—	1	1	—	—	2
Reactive depression	1	1	—	—	—	2
Manicdepressive psychosis	—	1	—	2	2	5
Total	19	20	20	20	18	97

to 68. Although nearly half the patients had had ECT before, none of them had received shock treatment in the nine months prior to inclusion in the study. Assignment of patients to the study was based on the clinical psychiatric judgment that shock treatment was indicated. Patients with significant organic defects of the central nervous system and patients who were considered more suitable candidates for some other form of therapy were excluded from the study.*

The group of 97 patients included 67 schizophrenic reactions, 14 with schizoaffective disorders, and 16 with depressive reactions. The distribution of patients by diagnosis in the various experimental groups is shown in Table 1.

Procedure.—The patients were assigned at random to one of five treatment groups: orthodox ECT, ECT plus succinylcholine (Anectine), ECT plus thiopental, thiopental alone, and nitrous oxide alone.

The regular ECT treatment involved the introduction of electric current into the brain, with loss of consciousness and grand mal seizure.† The ECT-plus-succinylcholine treatment differed from regular ECT only in having the major portion of the motor component of the grand mal seizure eliminated by the prior administration of 12-20 mg. of succinylcholine chloride. In the ECT-plus-thiopental treatment, the same elements were involved as in regular ECT except that unconsciousness was rapidly induced prior to each treatment.

The two nonshock treatment types, thiopental alone and nitrous oxide alone, both involved repeated, rapid induction of unconsciousness but no electroshock. The usual duration of unconsciousness was quite similar for all of the types of treatment, and the length of time spent in the recovery room was held constant.

Every effort was made to keep the patients from knowing which treatment they were receiving. Electrodes were applied to all patients, regardless of type of treatment, and a minimal amount of cutaneous electrical current (20 ma.) was briefly applied to the thiopental group. There was no indication that any patient was aware that he was not receiving any form of ECT, although some patients in the nonshock groups believed that they were receiving some new variation of ECT. The subjects were assigned to the treatment groups by one person, who had no knowledge of the patients and was not involved in their treatment.‡ No one who was concerned with evaluation knew what treatment the patient was receiving.

Treatment was given three times a week; generally a course of 20 treatments was administered to each patient. All patients participated in the regular hospital activities program, but no individual or group psychotherapy was given during the period of active treatment. The hospital program in which all participated and the attention received may have influenced the results to an unknown degree; but, at least on the objective level, these elements were the same for all patients. Once a patient was assigned to the study, he was systematically observed and tested in a variety of ways for a period of one week before treatment was initiated. Further testing was done periodically throughout the course of treatment, and at certain times after the end of treatment. This complicated testing schedule provided the opportunity to obtain a wide variety of psychological, biochemical, and physiological data reflecting pretreatment status, as well as changes occurring during and after treatment. The present report, however, is

* The bases for selecting patients are described more fully in an earlier publication.[3]

† An Electronicraft machine, Model #107, which produces a glissando-type sinusodial current, was used with electrodes applied frontotemporally.

‡ In a few instances the existence of spinal pathology necessitated assignment to either a nonshock group or ECT plus succinylcholine.

concerned only with the influence of the type of treatment on improvement and therefore utilizes only psychiatric evaluations and psychological test data§ collected before treatment and one month after treatment.‖ Results with respect to these additional factors will be reported in later publications.

The study has been in progress for about three years, the present report being based on 97 completed cases. An additional 45 cases were started but were dropped for a number of reasons, such as pretreatment improvement, refusal of treatment, elopement, etc.

Equation of Groups.—To determine whether the random assignment of patients to treatment groups resulted in reasonably well-equated samples, the distribution in these groups of 27 variables¶ which might have prognostic significance was determined. The five groups differed in composition to a statistically significant degree only in the degrees of nonverbal fear of ECT. This finding, however, cannot be interpreted as indicating a real bias, because one significant result out of 27 statistical tests would be expected on the basis of chance alone.

Results

Improvement Measures.—Three different methods were used to rate improvement one month after the end of treatment: psychiatric evaluation, the Lorr Psychiatric Rating Scale,[4] and psychological testing. A fourth measure of improvement was derived by combining the three ratings in such a way that a patient was judged to have improved if he was rated as improved by at least two of the three different methods.

Psychiatric status was evaluated clinically before and after treatment on a nine-point scale that was a function of both the degree of psychopathology and the impairment of function. The number of scale steps indicated the degree of improvement. The range of scores in the 97 cases was from an improvement of 8 scale-steps to a worsening of 3 scale-steps. The average score for the total group was 2.1 units of improvement. The scores were also divided into "improved" *vs.* "not improved" categories in order to compute improvement percentages. The "improved" category included all patients with scores of 2 or more units of change in the direction of improvement. This division point was chosen to minimize the effect of any lack of reliability in the ratings, and it also marked the approximate central point of the distribution. The improvement percentage for the total group was 49.4.

The second measure of improvement was the change in the Lorr Psychiatric Rating Scale.# This scale consists of ratings on 40 items made by psychiatrists on the basis of an interview, and 22 items rated by nurses on the basis of ward observation. Since both types of ratings were completed for only 71 patients, analysis was also made of the ratings made by the psychiatrists alone (82 cases).

The range of scores for the total Lorr Scale change was from improvement of 61 points to worsening of 27 points, the mean improvement being 14.2 points. The percentage of improvement for the total group was 52.1. To compute percentages of improvement, the distribution was divided at the median; i. e., the "improved" category indicated an increase of 14 or more points.

§ The following tests were administered to each patient: Individual tests: Wechsler Adult Intelligence Scale, Rorschach, Fisher Thematic Apperception Test, Bender-Gestalt, Brentwood Word-Chain Association Test, Hildreth Feelings and Attitudes Scale, Hildreth Psychological Change Scale. Group tests: Shipley-Hartford Scale, Grayson Perceptualization Test, Draw-a-Person, Saxe Sentence Completion Test, Minnesota Multiphasic Personality Inventory (MMPI).

‖ A complete list of the various factors studied and times of study appear in an earlier paper.[3]

¶ Diagnosis, Duration of Illness, Types of Illness, Age, Age at Onset, Premorbid Personality, Previous Shock Treatment, Degree of External Stress, Self-Expression, Projective Expression, Cognitive Speed, Motor Speed, Self-Esteem, Exaggerated Guilt, Fear of Shock, Expectation of Shock, Lorr Total Depression Factors, Lorr Total Schizophrenic Factors, Lorr Deviation, General Fearfulness, Degree of Fear—Verbal, Degree of Fear—Nonverbal, Attitude Toward ECT—Verbal, Attitude Toward ECT—Nonverbal, Funkenstein, Total Catecholamines, Serum Calcium.

A deviation score was used in preference to the morbidity score utilized in the preliminary report,[3] in accordance with recommendations of the author (personal communication).

When the doctors' Lorr Scale was analyzed separately, the range of scores was from an improvement of 46 points to a worsening of 27 points, the mean improvement being 11.0 points. The percentage of improvement for the total group was 51.2. This distribution of scores was also divided at the median in order to compute percentages of improvement; the "improved" category included all cases who improved 8 or more points.

Change in psychological status, based on 94 cases, was rated from an over-all evaluation of the test productions of the patient before and after treatment, the rating being made on a 5-point scale. The range of scores was from 2 (definitely improved) to −2 (definitely worse), the mean for the total group being 0.5. To compute improvement percentages, patients with scores of "definitely improved" or "slightly improved" were classified as "improved," while patients with scores of "definitely worse," "slightly worse," or "no change" were classified as "not improved." The percentage of improvement for the total group was 45.7.

The three different methods of rating improvement were in essential agreement; however, there was enough variation in the ratings of improvement according to which method was used to indicate that the different methods were measuring somewhat different aspects of improvement.*

These ratings of improvement were made one month after the end of treatment. Whether they reflect long-term or only temporary improvement cannot be determined without follow-up studies.

Results of the Different Treatments.†—Table 2 shows the percentages of improvement for the different treatment groups according to the "best-two-out-of-three" criterion of improvement. Regular ECT, ECT plus succinylcholine, and nitrous oxide appear to have the highest improvement rates; ECT plus thiopental, and thiopental alone, the lowest rates of improvement, for the total group of patients. According to the results of the χ^2-test, however, these differences are no greater than might occur by chance. ($\chi^2 = 5.93$, with P between 0.30 and 0.20.) When the groups are combined into "shock" *vs.* nonshock groups, the improvement percentages are very similar (Table 2). The associated χ^2-value of 0.56 indicates a probability between 0.50 and 0.30 that the difference is due to chance.

TABLE 2.—*Results of the Different Types of Treatment*

Treatment Group	Percentage of Improvement					
	Total Group		Schizophrenics		Depressives	
	N	%	N	%	N	%
ECT alone	19	63.2	11	45.4	8	87.5
ECT & succinylcholine	20	60.0	10	40.0	10	80.0
ECT & thiopental	20	35.0	17	35.3	3	33.3
Thiopental alone	20	35.0	15	33.3	5	40.0
Nitrous oxide	18	55.6	14	57.1	4	50.0
Shock groups	59	52.5	38	39.5	21	76.2
Nonshock groups	38	47.4	29	44.8	9	44.4
Total group	97	49.5	67	41.8	30	66.7

Thus, according to this consensus method of evaluating improvement (for the total group of patients), the types of treatment do not appear to differ in their therapeutic effectiveness. There is no more than a slight

* Further data bearing on the important question of what improvement measures are measuring will be presented in another report.

† Statistical Treatment of Results: The relationship of the different types of treatment to improvement was analyzed by two different statistical methods, the parametric analysis of variance technique and the nonparametric χ^2-technique. There was no evidence that the assumptions underlying the use of analysis of variance were violated by our data (i. e., none of the tests for homogeneity of variance yielded significant results); but, in view of the nature of the data, it was considered necessary to analyze the data also by the χ^2-method, which involves no assumptions about the nature of the variable of improvement. This method required that some of the scores be grouped in order to have categories sufficiently large for the technique to be appropriate. In order to avoid any possibility of error through the arbitrary division into categories, the scores were broken down in a number of different ways, and the statistical test applied to each breakdown. The treatment groups were also categorized into shock *vs.* nonshock groups.

and inconclusive tendency for certain types to be superior to others. The difference between the shock groups and the nonshock groups is certainly not a significant one.

χ^2-Tests were performed to determine the relationship between the different types of treatment and improvement as measured by each of the methods in turn. The improvement scores were condensed in each instance into either two (improved and not improved) or three (markedly improved, slightly improved, and not improved) categories. The same tests were also performed with the treatment groups dichotomized into shock and nonshock. The χ^2-value in each case was no higher than would be expected by chance alone, in spite of the presence of apparently large percentage differences, seen in Table 3. According to these tests, improvement was found to be independent of type of treatment, regardless of the method for measuring improvement.

The χ^2-technique is more defensible, but somewhat less precise, than the method of analysis of variance. In order not to overlook any information contained in the data, we also performed a single classification analysis of variance on the scores for improvement yielded by the three different methods of evaluation. (This statistical technique could not be applied legitimately to the improvement percentages based on the consensus of the three methods.)

The results of these analyses indicated that there were no statistically significant differences among the treatment groups in degree of improvement as measured by change in psychological status, change in the Lorr Scale, or change in the doctors' Lorr Scale.

The analysis of scores for improvement in clinical evaluation, however, yielded a variance ratio of 2.77, significant at less than the 0.05 level, indicating that the means of the treatment groups differed from each other to an extent greater than chance. When tests were performed to discover which group means actually differed, it was found that the ECT-plus-succinylcholine group had a statistically higher mean than any of the other groups with the exception of the regular ECT group. None of the other treatment types differed significantly among themselves.

These results are not entirely consistent, since one out of the four analyses of variance yielded statistically significant results. Although we were inclined to accept the χ^2-findings as a better representation of the true results, we felt it desirable to attempt to explain the one statistically significant finding.

It was noted earlier that no statistically significant bias existed in the placement of patients in the various treatment groups with respect to a number of variables, including the variable of diagnosis. However, as Table 1 indicates, the groups were not precisely equal in actual proportion of schizophrenics and depressives. The groups with the best improvement rates (ECT, ECT with succinylcholine) had the highest numbers of depressives. This raises the possibility that the results are actually influenced by this difference, even though the difference is not large enough to be statistically significant. This possibility is further borne out by the presence in our data of a statistically significant, although rather low, correlation between diagnosis and improve-

TABLE 3.—*Percentages of Improvement in the Different Treatment Groups*

Group	Method of Evaluating Improvement							
	Clinical		Psychological		Lorr Scale		Doctors' Lorr	
	N	%	N	%	N	%	N	%
ECT alone	19	57.8	18	61.1	13	76.9	15	73.3
ECT & succinylcholine	20	70.0	20	55.0	11	63.6	16	56.2
ECT & thiopental	20	30.0	20	45.0	16	62.5	18	50.0
Thiopental alone	20	35.0	18	22.2	15	26.7	16	31.2
Nitrous oxide	18	55.5	18	44.4	16	37.5	17	47.0
Shock group	59	52.5	58	53.4	50	67.5	49	59.2
Nonshock group	38	44.7	36	33.3	31	32.2	33	39.4
Total group	97	49.4	94	45.7	71	52.1	82	51.2

ment as measured by clinical change (0.24).‡

The analysis of variance was therefore repeated for the clinical-change scores of a smaller number of patients, the treatment groups being made exactly equal in proportion of depressives to schizophrenics. Although the rank order of the group means was unchanged by this procedure,§ the differences among the groups were now too small to be statistically significant.

It would appear that since our depressives tended to improve on clinical evaluation somewhat more than our schizophrenics, the slight overweighting of depressives in some of the groups gave those groups an unfair advantage.

Effect of Diagnosis.—The results reported thus far were based on the total group of patients, a group homogeneous with respect to judged need for shock treatment but heterogeneous with respect to diagnosis. The complete χ^2-analysis was repeated for two subgroups taken separately, the 67 schizophrenics and the 30 depressives (including schizoaffectives). The analysis of variance was repeated only for the clinical evaluation scores.

In no case was there any statistically significant difference. That is, when the schizophrenics were considered as a separate group, improvement (however measured) was not determined by the particular type of treatment or by whether the patient actually received shock. Table 4 shows the percentages of improvement for schizophrenics.

Similarly, when the 30 depressives were considered as a separate group, the improvement scores were not reliably affected by type of treatment, in spite of some apparently marked differences in improvement rates (Table 5). The percentages for the types of treatment and for the combined shock and nonshock groups are based on a very small number of cases.

In the ECT-plus-thiopental group, for example, one patient contributes 33.3 to the percentage figure. The test for statistical significances takes into account the low number of cases in each group. It is possible that such differences as were found might prove to be significant in a larger number of cases. However, for the schizophrenics, the number of cases is sufficiently high that we can place confidence in the likelihood of

TABLE 4.—*Percentage of Improvement in the Different Treatment Groups for Schizophrenics*

Group	Method of Evaluating Improvement							
	Clinical		Psychological		Lorr Scale		Doctors' Lorr	
	N	%	N	%	N	%	N	%
ECT alone	11	54.5	10	50.0	7	57.1	8	50.0
ECT & succinylcholine	10	60.0	10	50.0	7	57.1	8	62.5
ECT & thiopental	17	29.4	17	41.2	13	61.5	15	53.3
Thiopental alone	15	33.3	13	15.4	11	27.3	11	36.4
Nitrous oxide	14	57.1	14	42.8	12	41.7	13	53.8
Shock group	38	44.7	37	45.9	27	59.3	31	54.8
Nonshock group	29	44.8	27	29.6	23	34.8	24	45.8
Total group	67	44.8	64	39.1	50	48.0	55	50.9

TABLE 5.—*Percentages of Improvement in the Different Treatment Groups for Depressives (Including Schizoaffectives)*

Group	Method of Evaluating Improvement							
	Clinical		Psychological		Lorr Scale		Doctors' Lorr	
	N	%	N	%	N	%	N	%
ECT alone	8	62.5	8	75.0	6	100.0	7	100.0
ECT & succinylcholine	10	80.0	10	60.0	4	75.0	8	50.0
ECT & thiopental	3	33.3	3	66.7	3	33.3	3	33.3
Thiopental alone	5	40.0	5	40.0	4	25.0	5	20.0
Nitrous oxide	4	50.0	4	50.0	4	25.0	4	25.0
Shock group	21	66.7	21	66.7	13	76.9	18	66.7
Nonshock group	9	44.4	9	44.4	8	25.0	9	22.2
Total group	30	60.0	30	60.0	21	57.1	27	51.8

‡ To determine correlation, diagnosis was ordered with respect to predominance of depressive component; a positive correlation, therefore, signifies that improvement increases with a greater predominance of depression over schizophrenia. The other correlations between diagnosis and improvement were 0.19 for the consensus method, 0.13 for psychological change, and 0.06 for the Lorr Scale.

§ ECT plus succinylcholine, regular ECT, nitrous oxide, thiopental, ECT plus thiopental.

obtaining similar results with a comparable group of patients.

The possibility arises that the inclusion of patients with schizoaffective disorders in the depressive group confuses the picture. Inspection of the data, however, gives no support to this possibility. Although the numbers are too small for meaningful comparison, patients with schizoaffective disorders, if anything, improved even more than those diagnosed as depressive. The regular ECT group, which had one of the two highest improvement rates for depressives, contained six patients with schizoaffective disorders to two with pure depressions.

Comment

The results may be summarized as follows: The type of treatment or whether or not the patient had shock did not significantly influence the amount or percentage of improvement, however measured, for the group of 97 patients considered suitable candidates for ECT, for the 67 schizophrenics, or for the 30 depressives (including those with schizoaffective disorders).

There are several possible reasons for the absence of significant differences among the types of treatment. One possibility is that the effective therapeutic component of ECT is the repeated rapid induction of unconsciousness in the patient. This, most certainly, is a cataclysmic event both from the neurophysiological and from the emotional point of view. This hypothesis might be investigated further, using different methods of inducing unconsciousness, with the purpose of refining the therapeutic possibilities of such a treatment method.

Another possibility is that a second factor common to all of the treatment groups was responsible for improvement in these patients. Although the patients in two of the groups did not actually receive electroshock, they were told that they were being shocked. As far as we could determine, they believed it. It could very well be that the primary therapeutic agent is the psychological meaning of the treatment to the patient. When patients are questioned concerning their feelings about shock treatment, there is little doubt that they see it as a threat to their lives, judging from their comparing it to "going to the electric chair" or fearing "that they'll be burned to a crisp" or "never wake up." To some, it may fulfill desires for punishment, and to others, the hope for death and rejuvenation; and to others it may mobilize ego defenses and increased attention to reality in the face of a treatment that is perceived as a threat to the patient's very existence, or the desire to be the passive receiver of treatment. These subtle psychological variables, difficult to elucidate though they are, should receive more research attention. The influence of the unusual amount of care and attention which all receive could be studied further by including control groups given equal attention but no pretense of any specific type of treatment.

The improvement obtained in the patients could have been effected by factors outside the experimental circumstances, such as personality, environmental, or somatic variables. In this study, these factors were controlled in the sense that many of them were measured and found to vary at random among the treatment groups. There was no reason to assume that any of the unmeasured, but possibly influential, variables would show any systematic association with a particular treatment group. If the influence of these unknown factors is strong enough to overshadow the influence of the shock treatment itself in patients of this type, then further research should aim at delineating these factors.

The theoretical implications of these results lie in the field of suggestions for further research. The practical implication is that, for groups comparable to this one, the more traumatic components of ECT (electricity, convulsions) might be abolished without reducing therapeutic effectiveness.

It should be emphasized that conclusions from this study can safely be generalized only to comparable groups of patients. A possible objection to this study is that the

sample was heavily loaded with chronic schizophrenics, who might not be expected to improve regardless of treatment method. Yet these patients did improve. The overall improvement rate compares fairly well with figures quoted in the literature, even though we employed rather strict standards (i. e., requiring a change of 2 points rather than 1 point in clinical evaluation, and requiring 14 points' change in the Lorr Scale ‖). As indicated earlier, the patients were selected on the basis of clinical suitability for ECT. Patients for whom there was little hope of improvement were excluded. Patients similar to these are being given ECT regularly in hospitals throughout the country, especially in veterans' hospitals, with their progressively more chronic patient load. We had some difficulty in securing patients who had not had ECT within nine months, at this or another hospital. Since ECT is still being used extensively with patients of this type, our group of patients cannot be considered as unsuitable for use in studying ECT. If a group of patients with exceedingly good prognoses had been employed, significant differences in response to the different treatments might have been even less likely.

ECT is recognized as being a most effective treatment in relieving depression. At first glance, our results appear to conflict with the results of years of accumulated clinical experience. Our 30 depressives (including those with schizoaffective disorders) did not respond significantly better to the three ECT treatment types than to the nonshock types. Perhaps twice that number would have been enough to demonstrate statistically significant differences. (Even then, one would have to explain why nitrous oxide was better than ECT plus thiopental.)

Our group of hospitalized depressives is probably not comparable to many of the depressive groups reported in the literature, especially since we included "schizoaffectives." There were too few patients with depressions only to permit their statistical analysis as a special group (Table 1). It has already been noted that the schizoaffective patients improved as readily as did patients with depressive diagnoses. We suspect, also, that our depressives being Veterans Administration patients, had a larger component of character disorder than would be found in depressives in other hospitals.

On the basis of our results, it cannot be said that ECT is not the treatment of choice for depressives. We can only say that we did not find it to be differentially effective in our sample of patients.

Yet our results do not necessarily conflict with clinical experience, even if we could assume that these depressives were truly representative of all depressives. Our patients received either ECT or simulated ECT. If it should be the case, as the data suggest, that the effectiveness of ECT derives not from the electricity or convulsion but from either the repeated unconsciousness or the patient's belief that he is receiving shock treatment, then this contradiction is more apparent than real.

Summary

A study was conducted to determine the relative therapeutic effectiveness of the major components of electroconvulsive therapy: the electrical stimulation, the motor convulsion, and the repeated rapidly induced unconsciousness. Subjects were 97 hospitalized male veteran psychiatric patients, who were randomly divided into five experimental groups. Three groups received ECT; two received simulated ECT.

The types of treatment were regular ECT (electricity, convulsion, and unconsciousness), ECT with succinylcholine (Anectine) (electricity, unconsciousness with major part of motor component of convulsion eliminated), ECT with thiopental (electricity and convulsion, but with unconsciousness induced prior to treatment), thiopental alone (rapidly induced unconsciousness),

‖ It should be noted that a more liberal criterion for improvement would not have yielded significant differences among the groups; the analyses of variance indicate that the means did not differ.

and nitrous oxide (rapidly induced unconsciousness accompanied by anoxia).

Improvement one month after treatment was determined by psychiatric evaluation, psychological testing, and the Lorr Psychiatric Rating Scale.

There were no statistically significant differences in the therapeutic effectiveness of the five variations of ECT and simulated ECT. Nor was there any reliable difference in results between the combined shock groups and the combined nonshock groups. This lack of differential effectiveness was found not only for the total group but for the 67 schizophrenics considered separately, and the 30 depressives considered separately.

The results suggest that neither electrical stimulation nor motor convulsion is a necessary component of effective ECT. The therapeutic agent probably is one or a combination of the factors common to the five types of treatment: repeated rapid induction of unconsciousness, the psychological meaning of the treatment to the patient, or the unusual amount of care and attention involved in the experimental procedures.

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Voice Recognition as a Measure of Self-Attitude and Relatedness

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The human voice, recorded or heard on the radio, has been used in research concerned with personality judgments, communication theory, and psychotherapy. As a form of expressive behavior it has, like art productions and handwriting, a relationship to a person's mental and emotional characteristics.

The "interpersonal" psychologies hypothesize a dynamic relationship between a person's concept of himself and his acceptance of others. Research by Wolff,[7] Huntley,[5] and others[3] suggests a close bond between the recognition of one's own expressive behavior and the acceptance of a person by himself and by others. The present research reports on exploration of interpersonal relationships using voice recognition as a means of acceptance.

The experimental population consisted of 33 boys receiving intensive inpatient psychiatric treatment at the Astor Home for Children. Their ages ranged from 7 to 15. The boys were in good physical health and of normal intelligence. Diagnostically the behavior disorders, neuroses, and psychoses were represented. All children spoke the English language without foreign inflection, and none had pronounced speech defects.

Following Sapir,[6] we define the *voice* as expressive movement, in individualized pattern composed of the factors of pitch, rhythm, intensity, inflection, and vocal mannerisms. It differs from *speech*, which is the content of expression and includes the subject matter, the vocabulary employed, the grammatical structure, and the style of composition. In our study, by excluding the clues which could arise from individual differences in *speech*, we have attempted to study only the *voice* of the subject.

Voice-recognition test materials consisted of a tape containing the recordings of our subjects' voices, each saying the standard phrase: "Hello! How are you? I am fine." These recorded voices were presented for recognition in the following manner: *First of all*, each boy was asked to recognize his own voice from among five voices played back to him. The child was given five trials, with his own voice presented in a different position in each trial. He was asked to indicate whether each voice was or was not his own voice.

The *second* voice-recognition test consisted of presenting the entire series of voices saying the standard phrase, with the child instructed to attempt the identification of each voice.

The *third* test consisted of presenting this entire series of voices to each of 10 staff members, who were instructed to identify each voice.

The experimental procedures also included self-concept testing and sociometric selection. The results of the self-concept and sociometric procedures have been reported by Colvin[1,2] and Finneran.[4]

Self-concept testing was conducted by the method devised by Colvin; viz., materials consisted of 35 identical 2-in.-high profile silhouettes of boys' heads arranged in a horizontal line across one wall of a room. The subject was told that these silhouettes represented the boys of Astor Home standing in line in order of strength, and then in order of smartness, popularity, and how well-behaved they were. Each boy was instructed to locate himself in this line on each of these four dimensions. His self-concept rating was the sum of these four ratings.

Sociometric testing consisted of asking each boy to indicate which three boys he would prefer in each of four social situations and which three boys he would rather not be within each of four social situations, viz., in school, at play, in the

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dormitory, and as a best friend. Popularity and unpopularity scores consisted of the total numbers of times that a boy was selected and rejected, respectively.

Results

Correlations were made of the following seven factors, viz., the Profile Self-Concept score; the sociometric Popularity and Unpopularity ratings; the number of correct identifications of a boy's voice by himself, by his peers, and by the adults, and the number of times that a boy succeeded in recognizing the voices of his peers. These correlations indicated the following relationships and interpretations.

A. The success of a subject in recognizing his own voice correlated significantly with the success of his peers in recognizing his voice (0.50). Peers and adults recognized a subject's voice with statistically significant consistence (0.64). However, only a slight relationship was evident between the extent to which a boy's voice was recognized by himself and by adults (0.16). These findings suggest the interplay of two factors.

1. Some voices are easier to recognize than others, especially by peers and adults who have relatively impersonal, objective attitudes toward them.

2. Recognition of one's own voice is a relatively personal and subjective experience, self-recognition, and seemingly also self-acceptance, being more clearly associated with recognition, and seemingly also acceptance, by peers than by adults. These findings and their interpretation are consistent with the often-observed tendency of early adolescents to show greater deference to the attitudes and values of their peers than of their parents and other adults.

B. Statistically significant relationships were observed between Self-Concept and the recognition of a boy's voice by his peers ($r=0.36$; $\chi^2=2.84$) and by adults ($r=0.38$; $\chi^2=5.57$). If recognition of a person's voice is a measure of his acceptance by others, these findings present evidence of a close bond between self-concept and acceptance by others.

C. Ability of our subjects to recognize their own voices correlated significantly with the extent to which they recognized the voices of their peers (0.69). This finding probably is partially the result of consistency in the accuracy level of perception, or consistency in the level of reality testing. However, these findings also are consistent with the conclusion that our subjects recognize, and thus also accept, others to the extent to which they are able to recognize and accept themselves.

D. Correlations between Self-Concept and sociometric findings are low but suggestive of Self-Concept being a positive function of Popularity (0.27) and a negative function of Unpopularity (0.32). These findings again suggest a definite bond between attitude toward the self and the extent of acceptance by others.

Explanations of recognition or lack of recognition of a person's own forms of expression have been given by other researchers. These include the "familiarity" theory, Wolff's [7] "theory of repression" and unconscious projection of a "wish-image," and Huntley's [5] postulate of "self-esteem" and "ego-level." This research does not attempt to test the validity of any of the above theories, but the experiments of Wolff and of Huntley demonstrate that a simple familiarity theory is not able to account for the results they obtain. We have not endeavored to correlate performance on the test procedure with behavior or life history of the patients. These experiments offer evidence to support correlations of self-concept, self-knowledge, and recognition of self by peers. These formulas may be expressed generally by saying that the person who accepts himself more readily recognizes his forms of self-expression, and these forms are recognized by his peers to the extent the person is accepted by his peers.

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A Controlled Experiment of Glutamic Acid Therapy

First Report Summarizing Thirteen Years of Study

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Introduction

At the time of our last publication on glutamic acid treatment, in 1951, accurate appraisal of its effectiveness was difficult because of controversial findings as to degree and nature of changes following therapy. Since we had stressed intellectual aspects of improvement, it was natural for early investigators to follow that trend and to try to duplicate our results. Success or failure of therapy was usually judged in terms of point gains or losses on psychological retest, with emphasis upon group statistics rather than upon individual clinical change.

Several studies appeared, nevertheless, showing the value of glutamic acid in cerebral functioning (regardless of alteration or lack of change in intelligence following therapy), results of which suggested that further investigation of the drug was warranted. As early as 1948, for example, Waelsch [1] reported on the global effect of glutamic acid in a biochemical consideration of mental deficiency. "It seemed that the performance of the total personality rather than some circumscribed intellectual functions showed improvement." Continuing further elaborated study, Waelsch later reported [2] upon the role of glutamic acid and glutamine in brain tissue.

In a group of psychotic patients, Mayer-Gross and Walker [3] found that in hypoglycemic coma following insulin shock, injections of glutamic acid accelerated return to consciousness. Ewalt and Bruce [4] likewise reported that among 40 schizophrenics some temporary improvement was found in general, with motor activity definitely increased. The best results were obtained from patients with apathy where complaints of weakness and fatigue were most prominent. Interest in their surroundings grew under therapy. Similar findings were secured more recently in a group of 27 elderly, chronically hospitalized psychotic patients with poor prognosis, reported on by Himwich et al.,[5] in whom clinical improvement in behavior was wide in scope in the absence of significant gains on intellectual and motor tests, suggesting that different areas of functioning were affected. Of these, 16 patients improved in action, 12 in emotion, 9 in intellection, 8 in interpersonal relationships, 5 in thought processes, and 2 in insight.

Facilitation of cerebral functioning was also indicated by early results of experimental work with laboratory animals (rats). Following the lead of Zimmerman and Ross,[6] Albert and Warden [7] confirmed facilitation of learning by the supplementary feeding of glutamic acid. It is of particular interest, therefore, that recently Hughes and Zubek [8,9] reported two laboratory experiments repeating maze learning, in which a dull strain of rats, but not a smart strain, benefited from a supplement of monosodium glutamate. In the more recent paper (1957), Hughes and Zubek [9] also reached the following conclusions in testing permanency of glutamic acid therapy.

The results of the present experiment indicate that a difference between the glutamate-fed and control dull rats can still be observed in retest carried out one month and three months after the

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termination of the glutamic acid supplementary feeding. These findings are in line with those of Zimmerman and Burgemeister, who reported that a group of mentally retarded children showed an intellectual gain two years after the cessation of glutamate feeding. It would appear, therefore, that the effects of glutamic acid on maze learning and intellectual processes can be relatively permanent.

Modification of initial attitude has been one of the major gains noted in the work of more recent investigators, and it is now recognized that original reports, including our own, suffered from oversimplification and failure to emphasize (1) scope of psychological changes at the behavioral level regardless of alterations in intelligence, (2) intricacies of chemopsychological interaction, and (3) possible applications of glutamic acid to physiological, psychiatric, and general medical problems.

A factor of major importance in calling attention to the highly individualized action of medication and to the relative independence of intelligence and behavior has been the recent extensive and accepted use of chemotherapy in the treatment of mental disorders. Glutamic acid was, of course, the controversial precursor to this approach. Drugs such as reserpine, chlorpromazine, and methylphenidate (Ritalin), etc., have been shown to produce a great variety of behavioral changes, with and without alterations in intelligence quotients which are measurable by test. They have also accentuated the well-known methods of medicine which have been used for centuries, where clinical observation of a patient has served as a criterion of improvement in his condition, and where the patient has served as his own control. It has likewise been common knowledge in medical circles that academic psychological control techniques involving groups are not substitutes for observed and reported behavioral changes in a patient following therapy. The latter point is made clear by Katz and Kowaliczko,[10] who recently reported upon the action of glutamic acid, where psychological tests were omitted entirely because, as the authors state, "the day-by-day reaction of the patient to his environmental surroundings would appear to us to afford a more valid index of his condition. Comparison of the results of successive tests of one sort or another could offer evidence no more convincing than the change from a previously sluggish, apathetic, uncooperative patient who refuses to eat or to dress himself to the cheerful, cooperative, active individual after treatment." This is typical of the approach of more recent investigators with a realization that improvement following glutamic acid is essentially a medical problem. Where verification of results may be secured by the introduction of psychological tests, we believe that greater weight is given to clinical findings. Where verification is not possible, on the other hand, it is a definite mistake to discard any drug as ineffective on that basis alone.

We, ourselves, have reported upon the favorable action of reserpine in producing behavioral improvement in the absence of intelligence quotient rise on retest.[11] Certainly no one would discard the drug because intellectual changes observed could not be verified on test, as was done in the case of glutamic acid in many instances.

Because intelligence retest quotients remained unchanged following the administration of reserpine (a tranquilizer), in contrast to initial findings with glutamic acid (a cerebral stimulant), where definite improvement in retest intelligence test scores was recorded in our studies, we decided to compare the effectiveness, under experimental conditions, of these two drugs in producing intellectual and behavioral alterations. This was done by matching a group of mentally retarded children and adolescents with behavior disorders, for age, sex, and intellectual level, with a similar group of children, and by giving one group glutamic acid for a period of six months and the other group reserpine for the same time interval. A third group of patients to whom a placebo was administered was also included as a further control. Results of this experiment are reported upon in the present paper, which is the

first of several giving a summary of our findings with glutamic acid over the past 13 years.

Procedure

In order to compare the action of glutamic acid and reserpine in producing intellectual and behavioral changes during the first six months of therapy, a selected group of 150 children was given glutamic acid (experimental group). Children were matched by pairs for age, sex, and intelligence quotient at the beginning of therapy with a corresponding group of 150 children given reserpine (control group). As an additional precaution, a second control group of 50 matched cases received a placebo, making a total of 350 patients in the study.

The Stanford-Binet Intelligence Test (Form L, 1937 Revision)[12] and the Merrill-Palmer[13] or Pintner-Paterson[14] performance tests were given before and after the six-month treatment interval. Observations of behavior during the pre- and post-treatment psychological test sessions were made by the testing psychologist, who was not informed as to the type of medication being given to any patient. Observations of behavior were also recorded by the neuropsychiatrist at the time of each office visit.

Nature and Age of Cases

The chronological age range for the total group of subjects was 4 to 15 years, with an average age of 9 years 8 months for the glutamic acid group, 10 years 1 month for the reserpine patients, and 9 years 7 months for the additional placebo control cases. Fifty-nine per cent of the patients were boys and 41% girls. Pretreatment intelligence quotients showed averages of 59.13, 61.01, and 61.00 for the glutamic acid, reserpine, and placebo control groups, respectively.

Dosage

Since the optimal dosage has never been worked out clinically and biochemically except on a pragmatic basis, as indicated in our previous reports, we have continued to determine the correct amount of glutamic acid on the basis of clinical observation. Admittedly, therefore, the dose administered in all probability in most instances was too high rather than too low. This, in our opinion, would not tend to vitiate results, since a lower dose would make results more uncertain than a higher dose. This technique of drug administration could be followed with considerable confidence, in our opinion, because glutamic acid has never produced any serious untoward side-effects which would tend to condition the investigator to underdosage rather than overdosage. Therefore, we followed our usual technique of prescribing an original dose varying between 2½ and 5 grains (0.15 and 0.3 gm.) daily, depending upon the age of the patient, and of gradually increasing this amount every few weeks up to what we considered an effective dose, based on clinical observation. One could, of course, administer a fixed dose to all patients, a procedure which conventionally, and clinically, would be a more scientific method of doing it; but we felt that such a method of drug administration would be emphasizing group technique rather than individual treatment. Since much of the scientific evidence to date indicates that the effect of glutamic acid is a highly individualistic matter, it is our opinion that cases should be, as much as possible, treated individually rather than as part of a group, where individual differences would be lost.

The same general technique was used in the administration of reserpine except that an initially small amount was given to all patients and then increased by a uniform increment periodically, but, again, using clinical observation as a criterion of the effective dose. This technique has, of course, been borne out clinically in the use of all so-called "tranquilizers." In the present experiment an average of 0.75 mg. daily was administered, with an individual range from 0.2 to 1.75 mg., given in three divided doses.

Since there are inherent and unavoidable pitfalls in the popular double-blind technique of dosage in drug administration, as was recently pointed out by Tuteur,[15] of which we have, of course, been aware for many years, we decided to use a placebo which in size, shape, color, and taste more closely approximated the glutamic acid capsules rather than reserpine, since the former requires large doses and the latter is administered in relatively small amounts. In this way the experiment would be weighted against glutamic acid rather than in favor of reserpine.

Results

A. Psychological Test Results.—Verbal intelligence test results are given in Table 1,

TABLE 1.—*Pre- and Post-Treatment Verbal Intelligence Test Averages for Glutamic Acid, Reserpine, and Placebo Control Cases*

Group	No.	Av. I. Q. Before Treatment	Av. I. Q. After Treatment	Point Difference	Critical Ratio
Glutamic acid	150	59.13	64.62	5.49	4.15
Reserpine	150	61.01	62.32	1.31	0.82
Control	50	60.04	61.06	1.02	0.76

before and after the six-month experimental treatment period. A gain of 5.49 points in intelligence quotient is recorded for the group of 150 patients receiving glutamic acid for six months, a figure which is statistically significant, i. e., not due to chance factors. In contrast to this, a rise of only 1.31 points is seen for the reserpine group, and one of 1.02 for the placebo control cases, indicating negligible gains (Table 1). Retest averages and findings show that glutamic acid post-treatment scores were raised much higher than those of the reserpine-treated group, or of the placebo controls.

Results in Table 1 reveal differences between pre- and post-treatment means for each drug separately, however, and do not indicate whether point differences in these averages following therapy are significant so far as action of one drug over the other is concerned. Further analysis of data, therefore, was made, as shown in Table 2.

TABLE 2.—*Verbal Intelligence Test Point Differences and Critical Ratios After Treatment with Glutamic Acid, Reserpine, and a Placebo*

Group	Av. Point/ Rise in I. Q.	Differences Post-Treatment Averages	Critical Ratio
Glutamic acid Reserpine	5.49 1.31	4.18	3.09
Glutamic acid Placebo controls	5.49 1.02	4.47	3.10
Reserpine Placebo controls	1.31 1.02	0.29	0.21

It is clear from Table 2 that significant differences in intelligence quotient averages were obtained between the glutamic acid group and the reserpine group, and between the glutamic acid group and the placebo controls (critical ratio more than 3.00). Significant differences were not found between the reserpine-treated group and the placebo controls, suggesting that, under the conditions of our experiment, glutamic acid was much more effective in producing favorable retest intelligence results on verbal material than either reserpine or the placebo. This evidence is in keeping with previously reported studies,[16] where glutamic acid gave positive findings and reserpine negligible gains after therapy.[11,17] It is concluded, therefore, that for the group as a whole glutamic acid does, and reserpine does not, produce ideational changes which may be recorded on intelligence test after six months of treatment.

Performance test results (nonlanguage) following the six-month experimental interval are given in Table 3. Only a very

TABLE 3.—*Pre- and Post-Treatment Performance Test Quotients for Glutamic Acid, Reserpine, and a Placebo After Six Months; Point Differences, and Critical Ratios*

Medication	Av. P. Q. Before Treatment	Av. P. Q. After Treatment	Point Difference	Critical Ratio
Glutamic acid	58.80	61.13	2.33	1.12
Reserpine	59.00	60.80	1.80	0.94
Placebo controls	57.22	59.17	1.95	1.02

small difference in functioning on performance retest was noted (Table 3), regardless of the particular medication given. None of the gains was significant statistically, and, from a group standpoint, post-treatment performance on this series of motor tests was not facilitated by glutamic acid, reserpine, or a placebo. These findings agree well with those formerly reported for glutamic acid and reserpine, where it was more difficult in the case of glutamic acid to raise the performance quotient during the first six months of treatment than the verbal quotient. Reserpine has consistently failed to raise either verbal or performance retest scores significantly, in our experience to date, regardless of the time interval, when group statistics are used as a measure of success.

B. Clinical Results.—1. Glutamic Acid: Clinical observations of behavior were made by the neuropsychiatrist at the beginning of treatment and at the time of each office visit. Ratings were given after treatment on the basis of these observations, results of which are shown in Table 4 for the

TABLE 4.—*Clinical Observations and Notes of the Neuropsychiatrist Before and After Treatment with Glutamic Acid for Six Months*

Before Treatment Trait Rated	No. of Patients	Per Cent	After Treatment: Better No.	Better %	Same No.	Same %	Worse No.	Worse %
Aggressive, wilful	22	11	12	55	9	40	1	5
Anxious, tense, insecure	31	16	16	52	12	38	3	10
Distractible	36	18	29	81	7	19	0	0
Hyperactive	36	18	28	78	6	17	2	5
Irritable, negativistic	11	6	6	55	4	36	1	9
Out of contact, confused	10	5	2	20	8	80	0	0
Shy, withdrawn, quiet	25	13	15	60	10	40	0	0
Unresponsive, slow, depressed	25	13	19	76	5	20	1	4
Total	196		127		61		8	

group of 150 patients who received glutamic acid for a six-month period.

One hundred twenty-seven, or 64%, of traits rated clinically showed improvement after six months of glutamic acid therapy. Thirty-two per cent of the patients were judged to have no noticeable gains following treatment, and in 4% of the cases behavior appeared to be worse. Most benefit was recorded for the categories of distractibility, hyperactivity, unresponsiveness, slowness, and depression, with 81%, 78%, and 76% of the children, respectively, showing improvement when the observational method was used as a criterion for estimating success or failure of glutamic acid therapy. When patients were out of contact and confused, on the other hand, an improvement in observed behavioral patterns was recorded in only 20% of the cases. It is believed that because most of the latter patients were psychotic before treatment, they were at a disadvantage on glutamic acid. It has been our experience that glutamic acid treatment is not particularly effective when this serious type of dysfunction is present.

2. Reserpine: Clinical ratings by the neuropsychiatrist of observed behavioral changes before and after treatment with reserpine for a six-month interval are given in Table 5. These 150 patients received reserpine in a manner similar to the glutamic acid cases reported upon in Table 4.

Treatment with reserpine was estimated to have resulted in improvement in 106, or 57%, of the total number of behavioral traits rated by the neuropsychiatrist, with 37% remaining the same and 7% being worse following therapy. Most effect from reserpine medication was demonstrated in the anxious, tense, insecure, irritable, nega-

TABLE 5.—*Clinical Observations and Notes of the Neuropsychiatrist Before and After Treatment with Reserpine for Six Months*

Before Treatment Trait Rated	No. of Patients	Per Cent	After Treatment: Better No.	Better %	Same No.	Same %	Worse No.	Worse %
Aggressive, wilful	24	13	14	58	7	29	3	13
Anxious, tense, insecure	19	10	15	79	4	21	0	0
Distractible	30	16	17	57	12	40	1	3
Hyperactive	30	16	20	66	10	34	0	0
Irritable, negativistic	22	12	15	68	5	23	2	9
Out of contact, confused	15	8	9	60	6	40	0	0
Shy, withdrawn, quiet	26	14	10	38	15	58	1	4
Unresponsive, slow, depressed	21	11	6	28	11	53	4	19
Total	187		106		70		11	

TABLE 6.—*Percentages of Improvement Showing Most Striking Differences Between the Action of Glutamic Acid and Reserpine After Six Months of Treatment*

Behavioral Traits Rated	After Treatment	
	Glutamic Acid, % Better	Reserpine, % Better
Out of contact, confused	20	60
Shy, withdrawn, quiet	60	38
Unresponsive, slow, depressed	76	28

tivistic, and hyperactive categories. It is significant that the range of effectiveness was wide, with a low point of 28% in the unresponsive, slow, depressed group. The latter finding highlights differences in the action of glutamic acid and reserpine, which may be seen more clearly by consideration of Table 6.

Figures in Table 6 indicate that when children in our study were out of contact and confused at the beginning of therapy, most of whom were psychotic, much better results were obtained clinically with reserpine than with glutamic acid following six months of treatment. Sixty per cent of the reserpine group showed improvement, in contrast to only 20% of the glutamic acid series. When, on the other hand, they were shy, withdrawn, quiet; or unresponsive, slow, depressed, glutamic acid was much more effective than reserpine. In the latter case 76% of the glutamic acid children showed improvement in observed behavior, as opposed to only 29% of the reserpine group. Although the number of cases is small, findings support the hypothesis that glutamic acid has more of an activating action, while reserpine has more of a calming, or tranquilizing, effect.

Observations of the neuropsychiatrist for the second control group, of 50 cases receiving placebos, appear in Table 7.

In the placebo control group 21 out of 65 traits were rated as having improved after the treatment period (Table 7). Such a finding clearly shows limitations in the observational method for rating behavior and tends to reduce figures reported for the glutamic acid and reserpine patients. A considerable margin favoring these groups remains, however, when allowance is made for rating errors, the glutamic acid group retaining a lead of 31% and the reserpine group a lead of 24% over the average improvement for the placebo control group. It seems justifiable to assume, therefore, that the observational method had considerable value and that the action of both drugs was far superior to that of the placebo medication, as would be expected.

Toxicity

Even though glutamic acid was the precursor of "tranquilizers," it has the unassailed advantage of no serious side-effects. Infrequent gastric distress and hyperactivity, due to overdosage, result from the necessary empirical method of arriving at an optimal dose, but the majority of cases

TABLE 7.—*Clinical Observations and Notes of the Neuropsychiatrist Before and After Placebo Medication for Six Months*

Before Treatment Trait Rated	No. of Patients	Per Cent	After Treatment					
			Better		Same		Worse	
			No.	%	No.	%	No.	%
Aggressive, willful	10	15	3	30	7	70	0	0
Anxious, tense, insecure	9	14	2	22	5	56	2	22
Distractible	13	20	5	39	8	61	0	0
Hyperactive	13	20	6	46	5	39	2	15
Irritable, negativistic	4	6	2	50	1	25	1	25
Out of contact, confused	3	5	0	0	3	100	0	0
Shy, withdrawn, quiet	7	11	2	29	4	57	1	14
Unresponsive, slow, depressed	6	9	1	17	3	50	2	33
Total	65		21		36		8	

show no untoward side-reactions to medication.

Comparatively speaking, side-effects with reserpine, even though in terms of toxicity the drug is about the mildest of all "tranquilizers," were much higher and more pronounced than with glutamic acid. As listed in a previous publication,[11] these side-effects are as follows: drowsiness, diarrhea, nasal stuffiness, and irritability. Toxic side-effects on reserpine occurred in 7% of the cases studied, although it must be remembered that this figure is based upon a study of children, for whom the dosage is usually much lower. It is our impression from studying the literature on the action of reserpine on adults, particularly in mental hospitals, that this percentage of side-effects is much higher.

Comment

An impressive amount of research has been conducted here and abroad during the past several years regarding the effectiveness of glutamic acid in the treatment of mental retardation. A complete resumé of the literature on this subject is far beyond the scope of this paper, but it is of interest that, in spite of refinements in technique, introduction of controls, use of placebos, etc., results regarding the nature and degree of psychological changes are still controversial, as they were originally, but with more positive than negative findings. Among those obtaining positive results, either in improved intellectual functioning or behavior, are Harbauer and de Boor,[18] Kurland and Gilgash,[19] du Plessis,[20] Schwöbel,[21] Göllnitz,[22] Jaeger-Lee et al.,[23] Kane,[24] Zublin and Lutz,[25] Bergius,[26] and Hoven.[27]

In describing the pharmacopsychological effect of glutamic acid in four cases, Müller[28] concludes that results are in large part dependent upon basic personality structure and mood. He speaks in terms of "heightened awareness" following treatment and feels that glutamic acid can be used in increasing efficiency in certain appropriate cases, but that controls are necessary because normal experience may be affected adversely by the drug.

In a large number of cases of mental retardation, Koch[29] found some improvement from the use of glutamic acid, but points out that the complexity of the problem necessitates further study and that conditions must be defined carefully before therapy is attempted.

More recently, Rogers and Pelton[30] reported positive findings using glutamine in a group of retarded children. Pallister and Stevens,[31] on the other hand, found no improvement when Accent (a condiment of monosodium glutamate) was administered. Lombard, Gilbert, and Donofrio[32] likewise reported no improvement with the use of glutamic acid buffered with sodium citrate (Glutamicol) for seven months.

In a group of 101 children, including epileptic, mentally retarded, mongoloid, postencephalitic, and cerebral paralytic children, 29 raised their retest intelligence quotient over a period of 16 months to 4 years of glutamic acid treatment, according to Vasquez and Farago.[33] A diminution of hyperactivity, instability, and aggressiveness with greater sociability, better motor control, and lessening of strabismus, was among the observed benefits of therapy.

Work cited is typical of reports appearing generally, where it is clear that considerable benefit has been obtained in many cases following the glutamic acid treatment of mental retardation. The nature and degree of those changes must still be subjected to further study, nevertheless, before the effectiveness of glutamic acid may accurately be assessed.

While glutamic acid therapy is one of those not too infrequent situations in medicine where empirical clinical findings outpace and precede basic physicochemical explanations, this does not vitiate the validity of its use as a clinical tool. Historically speaking, similar situations have arisen in the past. No one knows how an anticonvulsant actually works and why a change in molecular structure changes anti-

convulsant activity. Actually, not much is yet known about epilepsy basically, in spite of the spate of literature on the subject. Knowing the intense emotional reaction engendered by our original findings, aggravated by wide and often sensational newspaper coverage, building up false hopes, we decided to withhold any further scientific publications on glutamic acid till time had permitted emotions to cool and additional work by other investigators would tip the balance of the scale in one way or the other. We feel that this time has now arrived. It is now commonplace to talk about psychoclinical drugs and their effect on behavior and intelligence. Medicine is no longer distressed by this concept; as a matter of fact, there are so many agents affecting behavior, and the claims are so optimistic, that it is necessary to restrain enthusiasm and point out that no drug is a substitute for training and insight.

In the case of glutamic acid, it is again necessary to emphasize that this chemical, like all the others, is not a substitute for tedious psychiatric work with a patient, but is merely a facilitator for the physician. As we have also said in previous publications, one cannot make a silk purse out of a sow's ear, or make an average person out of a defective child. Waelsch,[2] in his early investigational work, also warned against considering glutamic acid as a cure-all for mental retardation. Glutamic acid does, nevertheless, in many instances, facilitate learning and modify behavior.

Again, it should be emphasized, to avoid narrow fixation of the effect of glutamic acid upon mental retardation, such as occurred in the past, that glutamic acid has a broad and general action upon mentation, and that aspect of mentation reflecting itself in what we call behavior. This effect is variable in degree and reflects itself naturally in adults, as well as children; the psychotic and the aged, as well as the young. This has been demonstrated amply by the work of Himwich,[5] Ewalt,[4] and others on the psychotic. Improved mentation may, or may not, reflect itself in terms of increased intellectual function.

This paper, the first of three, concerns itself partly with increased mentation, as reflected by intelligence test results; but we are well aware of the limitations of these measuring instruments. The crux of the problem, as we see it, is basically not whether the intelligence quotient goes up or down. (It is well known that the intelligence quotient of many distressed persons increases when stress is alleviated.) The essence of the problem is the effect of glutamic acid upon mentation, and, through this, upon personality and behavior. We believe that the wealth of literature throughout the world now amply demonstrates this total effect.

Our two subsequent publications will deal with patterns of behavior and a final review of the broad therapeutic scope of glutamic acid as revealed in the reported literature, with its application to general medical problems.

From the standpoint of the basic physiochemical mechanism involved, glutamic acid appears to be part of the Krebs cycle, and it would be most reasonable to postulate that, in some way, the addition of this chemical, as part of this cycle, has a direct effect upon the nervous system. Some years ago, Nachmansohn[34] showed that glutamic acid had a definite influence upon the activity of acetylcholine, which itself is the principal chemical basis of nerve activity. He found that glutamic acid activates the enzyme cholineacetylase, which, in turn, synthesizes acetylcholine. This was a forerunner of much subsequent biochemical work on the glutamic acid-glutamine and aspartic acid-asparagine systems by Towers,[35] who in some instances found that glutamine had a remarkable effect in reducing the abnormalities of the electroencephalogram in epileptics, even though this was not always correlated with any significant reduction in seizures. More recently, Terner[36] likewise implicated these two systems in electrolyte transport in brain tissue. Still more recently, Woodbury, Koch, and

Vernadakis [38] studied the effects of diphenylhydantoin (Dilantin) and acetazolamide on concentrations of free amino acids in the brain. They found that the glutamic-acid and aspartic-acid concentrations and the glutamine and asparagine concentrations were increased by acetazolamide, while, in contrast, diphenylhydantoin decreased the glutamic- and aspartic-acid concentrations but also increased the glutamine and asparagine concentrations. It should be remembered, as we pointed out some years ago, that, physiologically speaking, epilepsy is largely a sudden interruption of conscious awareness, while mental retardation and the diminished mentation of the aged are a matter of constant, chronic and/or slow diminution of conscious awareness. Hence the interest of so many investigators with these two chemical systems as part of a much more elaborate, still unknown chemical system embracing the ultimate mechanisms of consciousness, is readily understood.

Summary

A selected group of 150 children treated with glutamic acid for a period of six months was matched with a corresponding group of 150 children given reserpine, and a placebo control group of 50 children, making a total of 350 cases studied. Comparisons were made as to the relative effectiveness of glutamic acid and reserpine in producing behavioral and psychological test changes, and striking differences were found.

For the glutamic acid group the average verbal intelligence quotient showed a significant point rise following six months of treatment, and the reserpine group showed only a small rise. The latter was true of the control group given placebos. Neither of the drugs or the placebo was successful in raising the performance scores beyond the realm of chance error.

Improvement rates of 64% and 57% were given to the glutamic acid and reserpine groups, respectively, on behavioral traits at the end of treatment, using the observational method as a criterion of success. Under these conditions, when children were out of contact and confused at the beginning of therapy, better clinical results were obtained with reserpine. When they were shy, withdrawn, quiet, or unresponsive, slow, depressed, glutamic acid was more effective than reserpine in alleviating symptoms. In cases classified as anxious, tense, insecure, or irritable, negativistic, hyperactive reserpine was the drug of choice, although glutamic acid gave results in a number of instances.

Findings in general agree with those of other investigators in showing assets and limitations of the observational method. Thirty-three per cent of control traits were rated as having improved at the end of the experimental period, placebo medication being given. Much higher ratings were obtained by the glutamic acid and reserpine groups, however, indicating definitely favorable action of each drug, well beyond the limits of personal bias or rating error.

Results support the hypothesis that glutamic acid has an activating action and reserpine a more calming, or tranquilizing, effect for the groups as a whole. Individual variability of response was extremely wide, nevertheless, making further study imperative. Definite overlapping in action of glutamic acid and reserpine was recorded in the individual case, showing that prescribed treatment in many instances was the result of the trial-and-error method.

From the standpoint of the basic physiochemical mechanism involved, glutamic acid appears to be part of the Krebs cycle, and it would be reasonable to postulate that the addition of this chemical, as part of this cycle, has a direct effect upon the nervous system.

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Analysis of Behavior Patterns Following Glutamic Acid Therapy

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Introduction

This paper is the second in a series of three summarizing 13 years of experience with the glutamic acid treatment of mental retardation and behavior disorders. In the first report [1] results of a controlled experiment are presented, comparing the effectiveness of glutamic acid, reserpine, and a placebo in producing intellectual and behavioral alterations and revealing the nature, as well as the degrees, of change obtained with each drug. Findings indicated considerable overlapping between action of the two drugs, with response broad in scope but highly individualized.

As we pointed out, emphasis in the past few years has shifted away from a narrow fixation upon change or lack of change in the intelligence quotient following treatment because of the realization that mentation is only one aspect of much broader Gestalten involving a wide variety of behavioral manifestations. In contrast to former reports, the crux of the matter has recently been attacked, namely, that glutamic acid treatment is essentially a medical problem, not an academic controversy. Improvement in observed behavior has rightly taken its proper place as the ultimate criterion of success. At present, for example, there is considerably more interest among investigators in the dynamics of action and underlying mechanisms operating in the individual case than there is in group statistics, where this individual responsiveness to therapy may be obscured. Under these conditions, much more favorable action of glutamic acid has been reported by many investigators recently than was apparent at the time of our last publication in 1951, before the present series of studies.

During the past several years we have continued to treat large numbers of children and adolescents with glutamic acid. As time progressed, we became increasingly impressed by the broad scope of action possible with the drug and the highly individualistic nature of responses to therapy. These observations, in turn, led to the realization that it was not only extremely difficult to predict in advance which patients would benefit most from the administration of glutamic acid but often impossible to isolate factors accounting for favorable results when they were obtained.

In order to clarify our ideas on individual reaction to therapy, i. e., individual differences as opposed to group findings, we subjected our material to detailed analyses involving numerous variables which seemed likely to have an effect upon intelligence retest scores and various aspects of observed behavior. This was done in an intensive search for factors, or patterns of response, which might predetermine success or failure of glutamic acid treatment. Our ultimate aim in breaking down findings in these ways was to differentiate at the beginning of treatment good from poor prognostic risks.

Pattern analyses of psychological test results, Rorschach records, and observed behavioral changes following glutamic acid treatment are reported upon in the present paper for a large number of patients over an interval of two and one-half years.

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Nature and Age of Cases

Six hundred fifty children and adolescents in private practice have been treated with glutamic acid during the past several years. After careful screening for cases with irregular medication, inaccuracies due to poor cooperation, infant psychological tests, adult tests, etc., the number of patients available for study on a basis comparable to our former work was reduced to 464. Analysis of factors and patterns reported upon here are for the latter group of 464 patients.

At the beginning of treatment with glutamic acid, the average chronological age of our group of children and adolescents was 9½ years, with a range in age from 3 to 16 years. Fifty-eight per cent of the patients were boys and 42% girls. The pretreatment distribution of verbal intelligence test scores spread from 31 to 96, or from low-grade defective to the average level.

Procedure

The Stanford-Binet Intelligence Test (Form L, 1937 Revision)[2] and the Merill-Palmer[3] or Pintner-Paterson[4] performance tests were given to all patients at the beginning of glutamic acid therapy and repeated after 6 months of treatment, and again after 1 year, 18 months, 2 years, and 2½ years of therapy. Rorschach protocols[5] were also obtained for each patient at these intervals.

Ratings of behavioral changes noted during psychological retest sessions were made by the psychologist, who was uninformed as to medication given. Ratings were also given by the neuropsychiatrist on observed behavior traits at the time of each office visit.

Dosage

As we explained in the first report of this series,[1] glutamic acid was administered empirically on a basis of clinical observation. This technique of drug administration could be followed with considerable confidence because glutamic acid has never produced any serious untoward side-effects which might invalidate the procedure. In our opinion, the dose administered, in all likelihood, was too high rather than too low, although we do not believe that this factor would vitiate results. In a low dose, it seems to us, there is more probability of uncertainty.

Original doses varied from 2½ to 5 grains (0.15 to 0.3 gm.) daily, depending upon the age of the patient. This dosage was increased gradually over a period of a few weeks, until an effective dose was suggested, the latter again being based upon clinical observation. It was felt that, in this way, individual treatment rather than group statistics would be facilitated. This seemed especially true because glutamic acid showed a very high degree of individual response to dosage. An average dose of 3½ grains (0.22 gm.) daily was given for the group as a whole.

Results

1. *Psychological Test Results.*—The average verbal intelligence quotient for the group was 59.07 at the beginning of glutamic acid therapy. This was raised to 64.71 after six months of treatment, or a gain of 5.64 points. Since an increment of only 0.74 point in quotient was obtained beyond one year of therapy, a "ceiling" was indicated with a leveling-off effect. For the entire two and one-half years of treatment the verbal intelligence quotient was raised a total of 7 points. It is of interest that all quotients for the group as a whole from six months to two and one-half years showed differences which were significant statistically, i. e., differences which were not due to chance errors.

Performance quotient averages were raised between 3.12 and 5.67 points for the two-and-one-half year interval. Although a positive trend was reflected, performance scores did indicate no significant changes at any of the interval points selected. Findings as a whole, therefore, reveal positive and statistically significant differences in scores measuring ideational change only, and hence favor the action of glutamic acid in the ideational area rather than in the motor field.

2. *Analysis of Psychological Test Patterns.*—Because individual differences are obscured in group averages, we approached the problem of finding differential patterns in a number of ways. One of these was to consider the scatter of point changes in verbal intelligence quotient following six months of treatment, the interval of greatest improvement.

Range of change on verbal test was wide, spreading from −5 to +24 points, as seen in Table 1. It is clear from this Table that there were many more positive than negative changes following six months of therapy. Almost one-fourth of the children

TABLE 1.—*Range of Verbal Intelligence Quotient Changes Following Six Months of Glutamic Acid Treatment*

N=464 Points	Percentage of Patients
18.00-23.99	1.5
12.00-17.99	5.5
6.00-11.99	23.0
0 - 5.99	61.0
−5.99-0	9.0

and adolescents in our study had intelligence test scores raised between 6 and 12 points, and almost two-thirds, between 0 and 6 points (Table 1). Of the latter, 7% had zero gain scores, however, leaving a total of 84% with some positive rise when all categories from 1 to 23.99 points, inclusive, are considered. Nine per cent of the patients showed losses in retest intelligence quotients after the six-month interval.

In order to determine whether pretreatment level of intelligence was related to success or failure of glutamic acid therapy, extreme cases were taken; i. e., the pretreatment intellectual level for that group of patients who gained 8 points or more after six months of therapy was compared with the group who showed no gains, or had actual point losses, in retest quotients during the same period. This criterion failed, however, to predict success or failure of glutamic acid treatment, as may be seen in Table 2.

Figures in Table 2 indicate that very little difference existed between the distribution

TABLE 2.—*Intelligence Quotient Distributions for Patients Receiving the Highest and Lowest Verbal Intelligence Retest Gains After Six Months of Glutamic Acid Therapy*

Intelligence Level (Pretreatment I. Q.)	8-Point Gain or More		No Gain or a Loss	
	No.	Per Cent	No.	Per Cent
30-39	3	4	3	4
40-49	7	9	4	5.5
50-59	14	19	24	32
60-69	16	21.5	14	19
70-79	18	24.5	19	25.5
80-89	14	19	8	11
90-99	2	3	2	3
Total	74		74	

of intelligence quotients for those who gained 8 points or more after six months of treatment and for those who did not show improvement in retest scores during the same period. When intelligence quotient averages were worked out for the two groups, the average initial verbal intelligence quotient for the patients for whom glutamic acid was most effective was 64.00. For the group showing no change or a loss, an average initial quotient of 62.50 was recorded. It is apparent, therefore, that pretreatment verbal intelligence quotient is not a good basis for differentiating between success or failure of therapy during the initial phases. As a further check, a Pearson *r* for the entire group was calculated, which was −0.34 between intelligence level and point change. The latter is negative and hence reveals no relationship between the two variables. This was also true for performance test scores. The only positive correlation found for the groups as a whole was one between verbal intelligence point change and age, where *r* was 0.21. This is positive, but too low to be of predictive value in the individual case.

Further divisions were made taking a variety of neurological and psychological factors into account, such as using point-change differences between patients with primary and secondary retardation; mongolism and nonmongolism; psychosis and nonpsychosis; patients with and without organic interference on initial test; patients with and without emotional interference on test, or patients with and without a combination of emotional and organic interference, etc. Under the conditions of study, none of these factors proved of differential value in predicting retest acceleration.

Some suggestive trends were secured, nevertheless, in the case of a group of psychotic patients and also in a group with organic involvement verified from a neurological standpoint, when the latter was combined with an initially organic Rorschach protocol. In the case of the psychotic group (68 patients), it was found that, both individually and as a unit, very little im-

provement on either verbal or performance test followed treatment with glutamic acid. Rorschach records also remained essentially unchanged. Removal of this group of psychotic children from the total group of 464 patients resulted in a marked increase in both verbal and performance test critical ratios.

In the group of 46 patients with organic involvement as judged by neurological examination findings and pretreatment Rorschach protocol, quite some improvement was recorded on verbal test, but very little on the performance, or motor, type of task. Elimination of this group from the total case load resulted in increasing the critical ratio for performance test to the point of significant difference, or to 3.02 (3.00 is minimal for significance). In many cases, therefore, the presence of organicity in a degree severe enough to be apparent on neurological examination and Rorschach test was a factor contraindicating improvement in the motor area following six months of glutamic acid treatment, and also over longer periods of time.

Beyond these few generalizations, response to glutamic acid therapy on psychological test appeared to be as highly individualized as suggested previously by empirical findings. It is clearer now, however, with a larger group of cases and detailed breakdown of data, that very complicated Gestalten are involved, which seem to include basic personality or constitutional differences, learning potential, previous training, socioeconomic status, etc., all, or any, of which may predetermine success or failure on psychological retest following treatment. Research done to date therefore strengthens the original hypothesis that glutamic acid therapy cannot be assessed adequately in the individual case until further careful study has been pursued.

The highly specific nature of response to therapy is highlighted in an item analysis of verbal intelligence test results following six months of glutamic acid treatment, where no two identical patterns of improvement were obtained for the total number of patients (464). Nevertheless, some items improved much more than others on retest. Test items showing the greatest improvement following six months of therapy are listed in Table 3, together with year levels, number of patients, and percentages of the total case load which these numbers represent.

TABLE 3.—*Stanford-Binet Items Showing Greatest Improvement on Retest After Six Months of Glutamic Acid Treatment*

Item	Year Level	No. of Patients	Per Cent of Total Case Load
1. Definitions	V	161	34
2. Vocabulary	VI	153	33
3. Mazes	VI	115	24
4. Counting	V	112	24
5. Vocabulary	VIII	101	23
6. Memory for sentences	VIII	94	20
7. Comprehension	VIII	94	20
8. Repetition of digits reversed	IX	85	18
9. Counting	VI	82	17
10. Mutilated pictures	VI	81	17

One hundred sixty-one, or 34%, more patients passed the Definitions test (Year V) after treatment than at the beginning of therapy. This item showed the most gain and was followed closely by Vocabulary at Year VI, where 153 patients, or 33%, were more successful on retest than initially. If the 10 highest items are scrutinized for qualitative changes (Table 3), it may be noted that word meaning, maze solving (foresight and planning), memory for numbers and sentences, comprehension requiring common sense and an understanding of social situations, counting, and mutilated pictures (discernment of missing details) constitute tasks involving complicated neuropsychological mechanisms. Most of these items may be classified under the heading of "abstract" thinking, rather than the more "concrete" type of reaction. Findings as a whole, therefore, indicate that improved retest scores rested heavily upon qualitative changes in mental functioning, including abstract aspects of thinking.

Since performance retests did not give statistically significant group differences, a

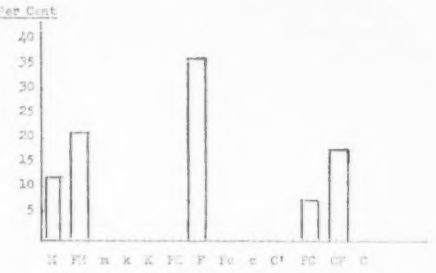
detailed analysis was not made of performance patterns. Where improvement occurred in the individual case, increased responsiveness reflected itself in faster reaction time and in a reduction of errors made. In many cases form perception was markedly improved by observation, indicating better discriminative abilities. In addition to measurable quantitative reductions in reaction time, it is apparent that qualitative changes occurred also on this type of test, as well as on verbal material, thereby emphasizing the broad scope of action of the drug.

Wide individual differences and lack of homogeneity among our patients regarding diagnosis, age, intelligence quotient level, and other factors make it somewhat impractical to combine Rorschach retest results for the entire group of 464 patients. In spite of these limitations, however, certain characteristics occurred with sufficient frequency as to reveal trends and to make some generalizations possible regarding areas most readily affected by the action of glutamic acid.

In interpreting findings, it seems worth while calling attention to the fact that most of the children in our series were seriously retarded, so that pretreatment Rorschach records in general were meager, perseverative, unproductive, and qualitatively poor. Paucity of ideas and inflexibility of thought were prominent. In addition, organic interference with thinking was recorded in about 15% of the patients tested, which revealed itself most frequently in minus (unacceptable) form quality, vague whole responses with little relationship to the blot material, and deficient organizational ability.

In the Figure Rorschach determinants are given which indicated most change following six months of glutamic acid treatment, as well as percentages of patients recording these alterations.

The Figure shows that most improvement occurred in the F determinant (36%), or in pure-form level. This indicates better form perception with fewer inaccuracies of discrimination, in keeping with verbal



Percentages of improvement in Rorschach retest determinants following six months of glutamic acid treatment.

and performance test results. In Rorschach terminology, this finding would also be interpreted as revealing capacity for better control following therapy, and less interference with thinking on an emotional or organic basis. The FM column (animal movement) showed an increase of 22%, suggesting a much more dynamic approach after treatment, even though much of this motivation was immature and primitive. If the latter finding is considered in connection with the 18% increase in CF (color-form) responses, it is clear that a much more outgoing and spontaneous reaction in the social area was recorded. The impulsiveness and explosiveness implied at times by this finding, which is typical of children's records (especially young children), are modified somewhat by the 7% increase in FC (form-color), which is a more rational, controlled, and socially adaptive kind of response. Usually an increase in FC is accompanied by an increase in M (human movement), and this is true of the present findings, where an addition of 12% in M is recorded. The latter insures a much more creative and mature type of reaction than was seen at the beginning of therapy. In addition, the number of popularly seen responses (not shown in the Figure) increased by 19%.

As a whole, Rorschach records revealed definite changes in personality after six months of treatment, which became accentuated even more as treatment continued. Better social or emotional adjustment was revealed in many cases and was reflected in

greater social responsiveness, better control, a more dynamic and spontaneous approach, and greater maturity than were seen in pretreatment records. Rorschach results agree essentially with verbal and performance test findings in revealing qualitative, as well as quantitative, changes following treatment. Although these alterations vary considerably from individual to individual, they also show rather clear-cut trends for the group as a whole.

3. *Clinical Improvement in Behavior.*—A. Ratings of Behavior by the Psychologist: Ratings of behavior were given by the testing psychologist during the test sessions when intelligence and performance material was administered, while the examiner was uninformed as to the type of medication given. This was done in order to determine whether improvement or lack of progress on test was related to behavioral changes which could be observed. Table 4 shows estimates of behavioral alterations as judged by the psychologist at the end of the first six-month period.

TABLE 4.—*Estimates of Alterations in Behavior During the Psychological Test Session at the End of Six Months of Treatment with Glutamic Acid*

Behavior	No. of Patients	Per Cent of Total
Improved	260	56
Same	158	34
Worse	46	10

Improvement in behavior during the psychological retest session following six months of treatment was recorded in 56% of the total cases studied. Thirty-four per cent of the children were rated as showing the same behavior as before therapy, and 10%, as showing less satisfactory conduct on retest than was noted during the pretreatment test session.

Inasmuch as 84% of the patients recorded a positive gain on intelligence retest, findings suggested a positive relationship between point rise in intelligence quotient and improvement in behavior following treatment, as observed clinically. For this reason, a correlation coefficient was calculated (biserial $r=0.45$). This figure indicates that a positive and fairly high relationship existed between improvement in verbal intelligence quotient following treatment and improvement in behavior, as was anticipated. Factors such as better attention, less distractibility, less negativism, etc., should be conducive to better retest response and be prone to accelerate the learning process. It is hypothesized, therefore, that a reduction in these emotional barriers accounted for quite some of the improved function seen on verbal intelligence retest.

B. Ratings by the Neuropsychiatrist: Behavior during office visits was rated by the neuropsychiatrist before, during, and after the six-month treatment period studied. Although the neuropsychiatrist was aware of the type of medication given, behavioral observations at the end of the treatment period were made before referring to charts giving that information. When it is considered that these 464 patients constituted but part of a much larger milieu, chances of remembering medication in the individual case were exceedingly small.

Numbers and percentages of patients showing various behavioral characteristics appear in Table 5, as well as numbers and percentages of children in whom these behavioral tendencies were judged to be better, the same, or worse following six months of therapy.

Incidence of improvement and better behavior following treatment varied considerably from a high of 68%, on shyness, to a low of 21%, on patients who were out of contact and confused. The range of children showing the same behavior following therapy extended from 29% to 72%, while from 0 to 7% of children were judged to be worse at the end of the six-month interval (Table 5).

For the group as a whole, ratings of the neuropsychiatrist showed an average improvement of 55%, which was close to the rating of the psychologist. Glutamic acid

TABLE 5.—*Numbers and Percentages of Children Showing Behavioral Characteristics at the Beginning of Treatment, and Numbers and Percentages with Better, the Same, or Worse Behavior Following Six Months of Glutamic Acid Treatment*

Pretreatment Behavior Rated	Patients		Post-Treatment					
			Better		Same		Worse	
	No.	%	No.	%	No.	%	No.	%
Aggressive, wilful	73	13	41	56	32	44	0	0
Anxious, tense, insecure	52	9	22	42	30	58	0	0
Distractible	86	15	49	57	35	40	2	3
Hyperactive	95	17	53	56	38	40	4	4
Irritable, negativistic	74	12	46	62	28	38	0	0
Out of contact, confused	53	9	11	21	38	72	4	7
Shy, withdrawn, quiet	72	13	49	68	23	32	0	0
Unresponsive, slow, depressed	68	12	45	66	20	29	3	5
Total	573	100	316		244		13	

was more effective in producing favorable results, where shy, unresponsive, negativistic, or distractible behavior appeared initially, than when children were out of contact or confused. As was reported formerly,[1] many of the children were psychotic, and clinical ratings are in agreement with formal test results in showing little benefit from treatment when a psychosis was present. Ratings leave no doubt, nevertheless, that results of glutamic acid treatment in terms of behavioral change are wide in scope and extremely variable from individual to individual, making generalizations difficult. There is considerable overlapping in all traits considered so far as improvement or lack of improvement is concerned (Table 5), and no category shows complete success or failure. At best, directional trends are suggested rather than unequivocal dichotomies.

Comment

A great many studies during the past several years have reported observed behavioral changes following glutamic acid treatment, but very few have attempted to define or to correlate interacting physiopsychological components. Lack of this knowledge makes it impossible at present to formulate principles or to state requirements which will assure beneficial action of the drug. In describing pharmacological effects of glutamic acid in four cases, Müller[6] concludes that results are in large part dependent upon basic personality structure and mood. He speaks in terms of "heightened awareness" following treatment and feels that glutamic acid can be used for increasing efficiency in certain appropriate cases, but that controls are necessary because normal experience may be affected by the drug.

Kane[7] also found some positive results following treatment and described unimproved and improved children's behavioral differences during the interval studied. The children with unimproved behavior showed hyperactivity, hyperexcitability, anorexia, insomnia, confusion, inability to concentrate, nervousness, and inclination to cry after four days of treatment. Children who later improved in intelligence quotient also increased their appetite, slept better, and showed improved concentration, self-confidence, and disposition. Two weeks after glutamic acid was discontinued, improved children tended to revert to their former behavior patterns. They also relapsed after three or four months when the dosage was reduced.

Although treated children could not be separated from others on the basis of quantitative test results, there was some evidence for qualitative changes in behavior in Bergius' study,[8] when the observational method was used. Increased energy and

stamina were noted in treated children; and where glutamic acid was effective, social responsiveness and energy increased, as well as mobility or readiness for tasks to be done. Pile [9] and Zabarenko and Chambers [12] reported that medication did not improve or substantially alter psychotic symptoms, personality, or intelligence quotients of patients treated, while Ewalt and Bruce,[10] Kitzinger, De Vere, Cartwright, and Shapiro,[11] and Himwich, Wolff, Hunsicker, and Himwich [13] noted improvement in personality, activity, and conduct in psychotics treated with glutamic acid.

It is clear from consideration of the preceding articles, which are typical of those appearing generally, that many different criteria have been used in the evaluation of glutamic acid therapy and that treatment has been given in a wide variety of conditions with considerable success. On the other hand, as Klingmüller points out,[14] it is not difficult to understand why determination of the exact action of the drug is still not possible, or knowledge available as to who will benefit most from therapy. Chemical relationships are still incompletely understood, and formulation of reactions at the physiological and psychological levels is even more complex. Problems of substance and qualitative integrative changes, etc., are some of the poorly defined biochemical and physiopsychological variables upon which precise evaluation rests. Although recent research has definitely taken the problem out of the academic area of controversy and into the medical realm emphasizing clinical improvement, where it belongs, the dynamics of action of glutamic acid appear almost as elusive today as when we last published on this subject, in 1951, before the present series of articles. The present studies do, on the other hand, serve to demonstrate the intricacies of behavioral patterns, the wide scope of possible action of glutamic acid, and the highly individualistic nature of response to medication, thereby pointing the direction for future research.

Summary

Analyses of patterns for 464 patients treated with glutamic acid for at least six months failed to reveal any particular factors which predetermine success or failure of therapy. The presence of very complicated Gestalten is suggested in the individual case, which seem to include such variables as differences in constitution, personality, learning potential, previous training, socioeconomic factors, etc., any of which may complicate the problem. A need for further research is evident from findings to date.

Verbal intelligence retest scores revealed significant gains following six months of treatment or more, while performance quotients showed less impressive rises. An item analysis of verbal intelligence test material showed that some tests improved much more than others after treatment. Those showing most change were wide in scope and heavily weighted with material classified as "abstract" rather than "concrete." Hence qualitative, as well as quantitative, improvement was recorded on psychological test.

A relationship was established between point rise and test behavior following therapy, indicating that reduction in emotional interference partially accounted for improvement in intelligence retest scores.

Observations of behavioral traits gave an average improvement of 55%-56% and indicated that glutamic acid was more effective where shy, unresponsive, negativistic, and distractible behavior occurred initially than where children were anxious, tense, or insecure.

Suggestive trends for the group were obtained in the cases of psychotic patients, and those with organic involvement severe enough to be detected by neurological examination and Rorschach protocol, where the least favorable prognosis was seen among the entire case load.

Present findings point away from narrow fixation on intelligence quotient changes as a criterion for evaluating glutamic acid treatment, and in the direction of clinical

improvement in behavioral traits and patterns, which are extremely wide in scope and highly individualistic. Understanding of the complicated dynamics of action involving biochemical, physiological, and psychological factors is necessary before glutamic acid therapy may be assessed adequately and shows the way for future research.

The implications of the final summary of our work over the past 13 years are in close agreement with the findings of other investigators throughout the world in the sense that the most reliable results are in the realm of behavioral changes following glutamic acid therapy and that I. Q.-point change is only an incidental or secondary factor, no doubt arising from removal or assuagement of emotional barriers. Contradictory findings over I. Q.-point change in the past have been due to overemphasis upon this narrow aspect of mentation rather than on observations of the total change in the individual patient. For this limited approach to the problem in the past, we accept our measure of responsibility.

11 E. 68th St. (21).

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Effects of Imipramine (Tofranil) on Depressive States

A Clinical and Psychodynamic Study

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Since the introduction of phrenotropic drugs in psychiatry, the major syndromes influenced by them have been those associated with excitation, elation, agitation, and, sometimes, anxiety. There has been, as yet, no satisfactory means for chemical control of depressive states. Amphetamines, effective in mild depression, have a transitory unpredictable effect and are also habit-forming. Iproniazid (Marsilid), one of the few promising antidepressants, may produce undesirable side-effects, and death, though rare, has followed its use.[1] While surveying different substances in this area, it was noted that Kuhn, in Switzerland,[2] had observed favorable results with an iminodibenzyl compound in 30 depressed patients. A preliminary trial with this substance[3] confirmed Kuhn's opinion. Concomitantly, Lehmann et al.[4] reached the same conclusions.

The present study was undertaken to observe more fully the effects of this substance (imipramine), which appeared to be a potent antidepressant and also to investigate the changes in psychodynamic states concomitant with its administration.

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Geigy Company, Inc., supplied the Imipramine (G.22355).

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Assistant Professor of Psychiatry (Dr. Azima) and Clinical Fellow and Assistant in Research (Dr. Vispo).

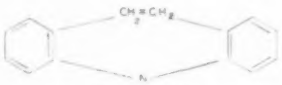
Material and Method

Imipramine is 5-(3-dimethylaminopropyl)-10,11-dihydro-5H-dibenz[b,f]azepine hydrochloride, with the accompanying structural formula, which is similar in many respects to that of phenothiazine.

Its toxicity in the form of L. D_{50} mg/kg. i. v. in the rat, mouse, and rabbit is similar to that of chlorpromazine. Isolated organ studies show that the drug has antihistaminic, antiacetylcholinic, antiserotonin, antiepinephrine and antinorepinephrine, and spasmolytic effects. In intact animals (rat and rabbit) imipramine exercises some hypotensive and hypometabolic influence, and it also potentiates hexobarbital (Evipal) anesthesia.[5] The drug in laboratory experiments acts like a sedative, with no stimulating effect.

Imipramine was administered to 145 patients, consisting of 126 with depressive states and 19 with other syndromes (Table). There were 35 men and 110 women, with an average age of 49 years. For 54 of these patients treatment was on either an outpatient or a private basis, and 91 others were hospitalized at an open psychiatric institute. About 90% of the patients received supportive psychotherapy concomitant with imipramine administration. Ten patients were closely observed for changes in psychodynamic state. They were seen from one to three times a week in short interviews lasting from 15 to 30 minutes, with the sole purpose of obtaining adequate descriptions of the presenting phenomenology from which to infer the alterations of psychic structure.

The drug was given orally in 98% of cases, and orally and intramuscularly in the rest. Intramuscular injection was given without dilution. The dosage ranged from 25 to 200 mg. daily, with an average daily dose of 100 mg. In the majority of hospitalized patients and in all of the outpatients



IMINODIBENZYL

PHENOTHIAZINE

Therapeutic Results of Imipramine

Diagnosis	No. of Cases	Improvement			
		Marked	Moderate	Slight	Nil
(*a*) Depressive states					
1. Psychotic					
Agitated	11	5	3	1	2
Nonagitated	29	12	11	5	1
Involutional	12	7	4		1
2. Neurotic	46	16	23	3	4
(*b*) Depressive states associated with					
Mixed neurosis	14	3	5	5	1
Hypochondriasis	4	1	1	1	1
Schizophrenias	6	2	3		1
Alcholism	4	2	2		
	126	48 (38.9%)	52 (41.2%)	15	11
(*c*) Other syndromes					
Schizophrenias	6			1	5
Character neurosis	1				1
Obsessive-compulsive psychosis	7				7
Anxiety neurosis	2				2
Conversion hysteria	1				1
Organic brain	2			1	1
Total	145	48	52	17	28

it was not necessary to go beyond a daily dose of 200 mg. for the therapeutic effect. Imipramine was the sole somatic treatment received by all but three patients, who were put on chlorpromazine therapy one week after imipraminization, owing to an increase in anxiety and some excitation. Imipramine therapy was discontinued or other somatotherapies were added if no appreciable therapeutic response was noted within three weeks. The follow-up period ranged approximately from five to nine months.

The criteria of improvement were considered under two categories: 1. Complete subjective and objective symptomatic relief. In cases of depression this was envisaged in four items: (*a*) disappearance of psychomotor inhibition; (*b*) disappearance of the experiential state of the spatiotemporal arrest, manifest partly in motor disinhibition and partly in the disappearance of feelings of hopelessness, helplessness, and doom; (*c*) disappearance of inferiority and guilt feelings, and (*d*) disappearance of self-destructive attitudes and feelings. 2. Complete objective and partial subjective symptomatic relief. This included items (*a*) and spatiotemporal acceleration of items (*b*) and (*d*) mentioned above, resulting in the resumption of predepression social effectiveness (as judged by the patient's performances and relatives' reports) without a complete subjective comfort. Patients were classified as markedly, moderately, or slightly improved if they fell into Category (1) or (2) or items (*a*) and (*b*) of Category (1), respectively. The patients showing slight improvement were not considered in the general therapeutic appraisal of the drug.

The following biochemical investigations were performed on the first 50 hospitalized patients: liver function tests twice a week; white blood cell count, differential count, and urinalysis once a week; blood pressure and temperature, pulse, and respiration readings twice a day. In the remaining hospitalized patients the blood count was performed once every two weeks, and the blood pressure and temperature, pulse, and respiration readings once a day.

Results

We shall discuss the results in two parts according to the depth and details of observations: gross and specific clinical results.

Gross Clinical Results.—These will be discussed under five headings: depressions, depressions associated with other syndromes, other syndromes, therapeutic maintenance, and side-effects.

1. Depressions: There were 98 more or less "typical" cases of depressive states which could be categorized into 52 instances of psychotic and 46 instances of neurotic depressions. The difference between psychotic and neurotic depressions, in our opinion, is a matter of intensity of experi-

ential events and the depth of regression, so that there is a continuum between them; however, for the sake of exposition and comparison, we have maintained an arbitary division.

Psychotic depressions consisted of 11 cases of agitated, 29 cases of nonagitated, and 12 cases of involutional states. General therapeutic response was marked improvement in 24 patients and moderate improvement in 18 patients. There was no difference in responsivity between agitated and nonagitated patients. The latter showed as good a response as the former. Of 46 neurotic depressed patients, 16 showed marked and 23 moderate improvement. Thus, out of 98 with uncomplicated depressive states, 81 (82.6%) showed significant improvement. It should be noted that if imipramine had not been used all the patients with psychotic depressions, and probably many with the neurotic depressions, would have been put on electric shock therapy. Several of the patients who received electric shock had an inadequate period of imipramine trial (one week), or the therapist thought it too risky to wait because of self-destructive tendencies. Another important point of note was that 22 patients (18 with psychotic and 4 with neurotic depressions) among those with typical depressed states had a previous history of many hospitalizations and had been treated with all forms of somatotherapy, including EST, in five without any effect. With imipramine therapy 12 of these patients showed marked and 8 moderate improvement, among them 4 of the 5 refractory cases. One case remained nonresponsive to imipramine, and this was a case of chronic neurotic depression of 20 years' duration. These observations led to the impression that imipramine seemed superior in effectiveness to EST in the majority of instances.

Finally, it may be worthy of note that there were two instances of periodic premenstrual depression which markedly improved under imipramine therapy, and at the time of writing these patients' premenstrual depression of many years has not recurred for six months.

2. Depression Associated with Other Syndromes: There were 28 patients in this category, consisting of 14 with mixed neuroses ("borderline states"), 4 hypochondriacs, 6 schizophrenics, and 4 alcoholics, in all of whom depression was a part of the phenomenology.

Of 14 with mixed neuroses, 8 showed significant improvement (3 marked and 5 moderate); of 4 hypochondriacs, 1 showed marked and 3 moderate improvement, and of 6 schizophrenics, 2 showed marked and 3 moderate improvement. The improvement seemed to have occurred exclusively in the depressive component of the phenomenological picture, with no change in paranoid, obsessive-compulsive, or hysterical aspects. This was particularly evident in four alcoholics, who showed marked improvement in their subjective feelings and abandoned the use of alcohol. In these patients alcohol was used exclusively to alleviate the feelings of depression. All of them ingested alcohol periodically, and in a very rapid way ("gulping the stuff down"), to get relief of this feeling. It seemed that imipramine had eradicated somehow this depressive core, and thus eliminated the necessity for alcoholic intake as a defense. This result is not surprising if we consider the similarity of psychodynamic problems in depression and addiction (see "Comment").

In general, out of 28 complicated depressive states, 19 (67.8%) showed appreciable improvement.

All in all, among 126 patients with depressive states (98 uncomplicated and 28 complicated), 100, i. e., 79.29%, showed significant improvement (48 marked and 52 moderate).

3. Other Syndromes: In this category there were 19 cases: 6 schizophrenia, 1 character neurosis, 7 obsessive-compulsive neuroses, 2 anxiety neuroses, 1 conversion hysteria, and 2 organic brain syndromes. Only one of the organic cases showed moderate improvement attributable to a better utilization of aggressive energy. The

smallness of the samples of nondepressed patients was due to this apparent ineffectiveness of imipramine in such conditions.

4. Therapeutic Maintenance: Regardless of the dosage regulation, there were three points worthy of note: (1) therapeutic lag, (2) long-term maintenance treatment and (3) rapid relapse and remission after the cessation and resumption of imipramine, respectively.

A certain lag in the therapeutic response was noted in all patients after the onset of imipramine therapy. About 10% of patients responded within three days, 30% within the first week, 30% within the second week, and the rest within the third and fourth weeks. Intravenous administration of the drug had no particular effect. The duration of treatment cannot be definitely stated at present. Kuhn and Lehmann [2,4] are of the opinion that the drug should be used as long as the natural course of the depressive episode is thought to last. This being very problematic, our impression led to the temporary conclusion that a period of three months after the symptomatic relief should be the optimum length of a maintenance therapy, after which the drug should be discontinued gradually within 10 days. Almost all patients whose treatment was discontinued after the first month of imipramine relapsed into their previous depressive state. The point of note, however, was the rapidity of relapse and remission when the patient resumed his imipramine intake. The relapse in several instances, in which patients stopped the treatment because of symptomatic relief, occurred within 12 hours. Remission of the depression could be obtained in these cases within 24 hours after the resumption of imipramine intake. This is in contrast to the initial therapeutic lag. The reasons for this may be threefold: 1. The original remission is due to suggestion effect, transference improvement, or other psychodynamic mechanisms. 2. A certain optimum level of imipramine saturation is necessary in the body or in certain neuronal sets, below which the depressive state will return; but to counteract it an addition of only a small amount of the drug is necessary. When this is added, the optimum level of imipraminization is rapidly reached and a remission occurs. 3. The rapidly relapsing and remitting patients are among those 10% who originally do not show a long therapeutic lag.

5. Side-Effects: These were of minor consequences, infrequent, and decreased or disappeared solely with the decrease of medication. Only in two cases was the drug discontinued, in the one because of exacerbation of a chronic eczema and in the other because of sleepiness, which prevented the patient's social functioning.

In order of frequency, side-effects consisted of dry mouth (about 20%), perspiration (about 10%), slight tremor of upper extremities (in about 15% of patients receiving more than 50 mg. daily), dizziness and blurred vision (5%), pruritus and skin rash (3%), nausea and vomiting (3%), and a rise in alkaline phosphatase (2%).

There was one case of hypotension, and one patient who was suffering from chronic eczema and ulcerative colitis experienced an exacerbation of both the skin and the bowel conditions.

Specific Clinical Results.—These were obtained from the close observation of 10 patients who responded favorably to the treatment. In these patients, concomitant with imipramine administration, the following more or less specific changes seemed to occur.

1. Disappearance of Feelings of Guilt: It was noteworthy that the changes seemed to have occurred in this particular form of anxiety, which is the feeling of guilt and which involves aggressive drives and their direction and relation to different parts of the psyche. Anxieties of other form remained unchanged. This was clearly seen in anxiety neuroses and mixed states. The anxiety of anxiety neuroses did not change, and in mixed states the only part of the clinical picture which seemed to have been altered was the depressive component.

2. Change from Feelings of Helplessness to Those of Hopefulness: This was closely connected with the relief of guilt feelings and also indicated, phenomenologically speaking, an "opening" into the world which, dynamically speaking, could be seen as the regaining of the possibility of libidinal investment of external objects.

3. Change from a Relatively Excessive Painful Preoccupation with Internal Happenings (Internal Object Relations) to a Relatively Optimal Preoccupation with External Happenings (External Object Relations): This was apparent in a decrease in the intensity of complaints ("I am going crazy"; "there is something wrong with me"; "I keep thinking and thinking about myself," etc.); an increase in spontaneity and responsiveness; an increase of what was expressed by one patient as "outgoingness," associated with an increasing interest in the environment, i. e., home, work, etc.

4. Appearance of Elation (Eight Patients), Hypomanic State (One Patient), and Manic State (One Patient): The elation was an exaggerated state of well-being, which gradually, within about three weeks, normalized itself. The hypomanic and the manic states occurred in patients with a previous history of manic-depressive swings.

5. Increased Ability to Express Aggression: It seemed that aggression, instead of being turned inward ("I am bad"; "I am no good") could be turned outward ("I am so mad"). This was apparent in the disappearance of suicidal ideas, appearance of bouts of anger, and an increased desire to "do things," and also to be "outgoing," as was mentioned above. In two instances the bouts of anger were particularly conspicuous because they occurred in patients who had been suffering for years from mild depression and feelings of inferiority, never capable of manifesting overtly any anger. A corroborative evidence was the disappearance of headaches in almost all instances where this symptom was present. The role of repressed aggression in the psychological etiology of headache being of importance, it is felt that the possible release or shift of aggressive energies under imipramine may explain the headache-relieving effect of the drug in certain instances.

6. Disappearance of the Need for Alcohol Intake: This occurred in four patients who were using alcohol to get relief from feelings of depression. These patients had received all kinds of drugs before, without any benefit. Under imipramine, for the first time in many years, their bouts of depression, with subsequent need to consume alcohol, did not occur.

7. Appearance of Basic, Predepressive Personality Patterns: This was particularly apparent in relatively recent (within two years) depressions. Patients with hysteria, obsessive-compulsive neuroses, and character disorders who had become depressed, for a variety of reasons, returned to their former states after the depression was eliminated from the clinical picture. No change in the predepression personality structure could be initiated. This was also true (as was mentioned above) for patients with anxiety neuroses, hysterias, obsessive-compulsive neuroses, and character disorders without depression, who remained unaffected by the drug.

Comment and Conclusions

The above data indicate that imipramine has a powerful antidepressant activity. If further trials show the same level of efficiency as was observed in the present series of cases, it can be stated that a turning point in the symptomatic improvement of the depressive states by pharmacotherapy has been reached. This will lead to a considerable decrease in the use or elimination of electric shock in these states.

From a theoretical point of view the mode of action of imipramine remains to be considered. This can be done within two frames of reference: organic and dynamic.

1. *Organic Hypotheses.*—The present investigation being solely clinical, there is very little, if any, comment which can be made about the organic mode of action of

imipramine. However, the following observations may give certain clues concerning the organic mode of action of imipramine.

(*a*) Similarity of the chemical structure of imipramine to phenothiazines, particularly promazine or chlorpromazine; (*b*) marked differences in clinical effects between imipramine and phenothiazines. The latter substances have no alleviating effect on depressive states, sometimes produce them, and more particularly counteract mania and excitation, elation, and sometimes anxiety states. In two instances in which a manic state occurred in patients whose depression had been relieved by imipramine and in five other instances in which certain degrees of agitation and anxiety occurred, the addition of chlorpromazine successfully normalized the clinical picture.

From these observations it may be inferred that imipramine either has an antiphenothiazine effect or acts on a different neuronal system. Considering that the central reticular activating system has both an inhibitory and an excitatory component, it may be conjectured that imipramine influences the inhibitory and chlorpromazine the excitatory component of the system, or they act antagonistically on these components, according to their presenting state at the time of drug administration. Of course, difficulties arise when one wishes to correlate directly the excitation and inhibition in the physiological sense to similar states from the psychological point of view. In addition, the states of mania and depression are not merely states of excitation and inhibition for which suitable physiological correlates can be found. Their complexity, from an experiential point of view, surpasses any purely physiological oriented conception.

2. *Dynamic Hypothesis.*—As we have pointed out elsewhere,[6-8] in all psychophysiological studies the ultimate problem is the ever-present dilemma of body-mind relationshp. In psychopharmacology this problem can be posited by asking: How does the administration of a chemical substance produce an alteration in a psychodynamic state resulting in a change in or relief of certain clinical symptoms? To say that a drug influences the reticular system, or acts as an antimetabolite, does not answer the question. For us the search for locality of influence or chemistry of change as such cannot clarify the matter of psychological alterations concomitant with pharmacotherapy. It is in the psychodynamic framework itself that the solution must be sought. We feel that the psychoanalytic framework provides adequate conceptual material for this purpose, and it is in the economical principle of the mind where an explanatory and linking concept may be found. The concept most suited seems to us to be that of cathexis or cathecting energies which involve both drives and object relations, there being no uncathected, uninvested psychic energy. We are also led to this conclusion because epistemologically it is simpler to maintain that a chemical substance affects drives which have an organic source rather than a psychological construct, such as ego. A change in the organic sources of drives, regardless of their neurological topography, produces a shift in the energetics of the mind, in cathecting energies and their topographical investment.

From the observations mentioned above under the "Specific Clinical Results," we think that the following temporary inferences can be made as to the changes in psychodynamic state: 1. Concomitant with imipramine administration, a temporary shift of aggressive cathecting energies seems to occur. The principal change appears to be in the direction of aggression from inside to outside. 2. This shift affects in particular the internal object system of control (superego elements). In this connection should be noted the disappearance of the need for alcohol intake in imipramine-treated patients and the role that superego concept plays in the explanation of depression and addiction.[9] 3. This leads to a readjustment of libidinal investment. 4. No definitive alteration of basic personality structure occurs, and the economical

shift involves only the recent imbalances of psychic economy.

Summary

Imipramine, an iminodibenzyl derivative, was given to 145 patients, consisting of 126 with depressive states and 19 with other mental syndromes, with an average oral daily dose of 100 mg. and an average duration of three months.

The depressive states consisted of 98 "typical" and 28 atypical cases. In the former group 82.6% showed marked to moderate improvement and in the latter group 67.0%.

There was a therapeutic lag of three days to three weeks before the clinical response would become manifest. The optimum period of therapeutic trial was about three months. Side-effects were minimal.

The specific changes concomitant with imipramine administration were investigated in 10 closely observed patients. These were the disappearance of feelings of guilt; a change from feelings of helplessness to those of hopefulness; a change from relatively excessive preoccupation with internal object relations to a relatively optimal preoccupation with external object relations; appearance of elation in eight patients, hypomanic state in one patient, and manic state in another; an increased ability to express aggression; the disappearance of the need for alcohol intake in four alcoholics; the lack of alteration in basic, predepression personality structure, which reappeared after the relief of depression. Based upon these observations, a dynamic hypothesis was forwarded that concomitantly with imipramine administration a change in the direction of aggressive drives and aggressive cathecting energies seemed to occur in relation to the internal object system of control (superego elements).

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Announcement

The ARCHIVES OF NEUROLOGY AND PSYCHIATRY was first published in 1919. At that time neurology and psychiatry were considered related subject fields and it was thought one journal would serve both adequately.

Over the years, psychiatry has been emerging as a distinct specialty. The volume of literature has increased to such an extent that official publications reporting psychiatry either could not absorb it or felt the need to condense the material to accommodate more contributions. Psychiatrists began to feel also that the ARCHIVES OF NEUROLOGY AND PSYCHIATRY should allot more space to psychiatry, that its emphasis over the years had been neurological.

In July, 1956, an effort was made to give equal emphasis to both neurology and psychiatry by dividing the ARCHIVES OF NEUROLOGY AND PSYCHIATRY into a two-section journal, with an editorial board for the Section on Neurology and a separate board for the Section on Psychiatry. This division had the effect of reducing the number of pages devoted to neurology, and the result was late publication dates for accepted articles, with the natural development of a large backlog. More psychiatric manuscripts were now submitted to the ARCHIVES, and only very high editorial standards and a high rate of rejection prevented a large backlog from forming.

The final development is to publish two separate journals. The division is prompted by the demand by both neurologists and psychiatrists for more text pages; by the neurologists, who feel the quality of a journal devoted exclusively to neurology can be much improved, and by the psychiatrists, who believe it is more realistic to recognize neurology and psychiatry as distinct clinical specialties. Consequently, July, 1959, will see the introduction of these two journals—the *A. M. A. Archives of Neurology* and the *A. M. A. Archives of General Psychiatry*.

Books

BOOK REVIEWS

L'exploration chirurgicale stéréotaxique du lobe temporal dans l'épilepsie temporale. By J. Talairach, M. David, and P. Tournoux. Price, ? Pp. 132. Masson & Cie, 120 boulevard Saint-Germain, Paris 6e, 1958.

This study consists of two parts: (1) an anatomical part which treats of the system of reference which the authors have adopted for stereotaxic interventions on the most important temporal structures, and (2) a surgical part describing their stereotaxic apparatus and the operative technique used. The text is confined strictly to the description of surgical technique concerned with stereotaxic exploration of the temporal lobe. There is no description of the techniques used for exciting or registering the activity of the structures. It is stated that these will be dealt with in due course by Dr. Bancaud and M. B. Dell.

The first part contains a series of 56 plates showing serial sections of the temporal lobe in sagittal and frontal planes. These plates are excellent. Only one criticism might be made: It is not clear what is the exact level of each section or what interval separates them. Accompanying the plates is a series of diagrams showing the range within which may be found the important structures in relation to the basal planes of the instrument.

In the second part there is a very clear account of the authors' stereotaxic instrument and the methods of its employ. Added is an interesting chapter on anesthesia. The authors state that they have never had an infectious or hemorrhagic complication.

The authors direct their instrument by measurements from the shadow of the temporal horn of the lateral ventricle established by roentgenography after intraventricular injection of Lipiodol. They state that their researches tend to confirm the variability of expression and localization of epileptic foci in temporal epilepsy and also the difficulties of interpretation. They bring important data for the therapy, which has already given more than satisfactory results, with a minimal operative risk, small lesions, and insignificant complications. They recommend the method as a desirable substitute for open operation and gross lobectomy. We will look forward to the publication of their physiological data and results.

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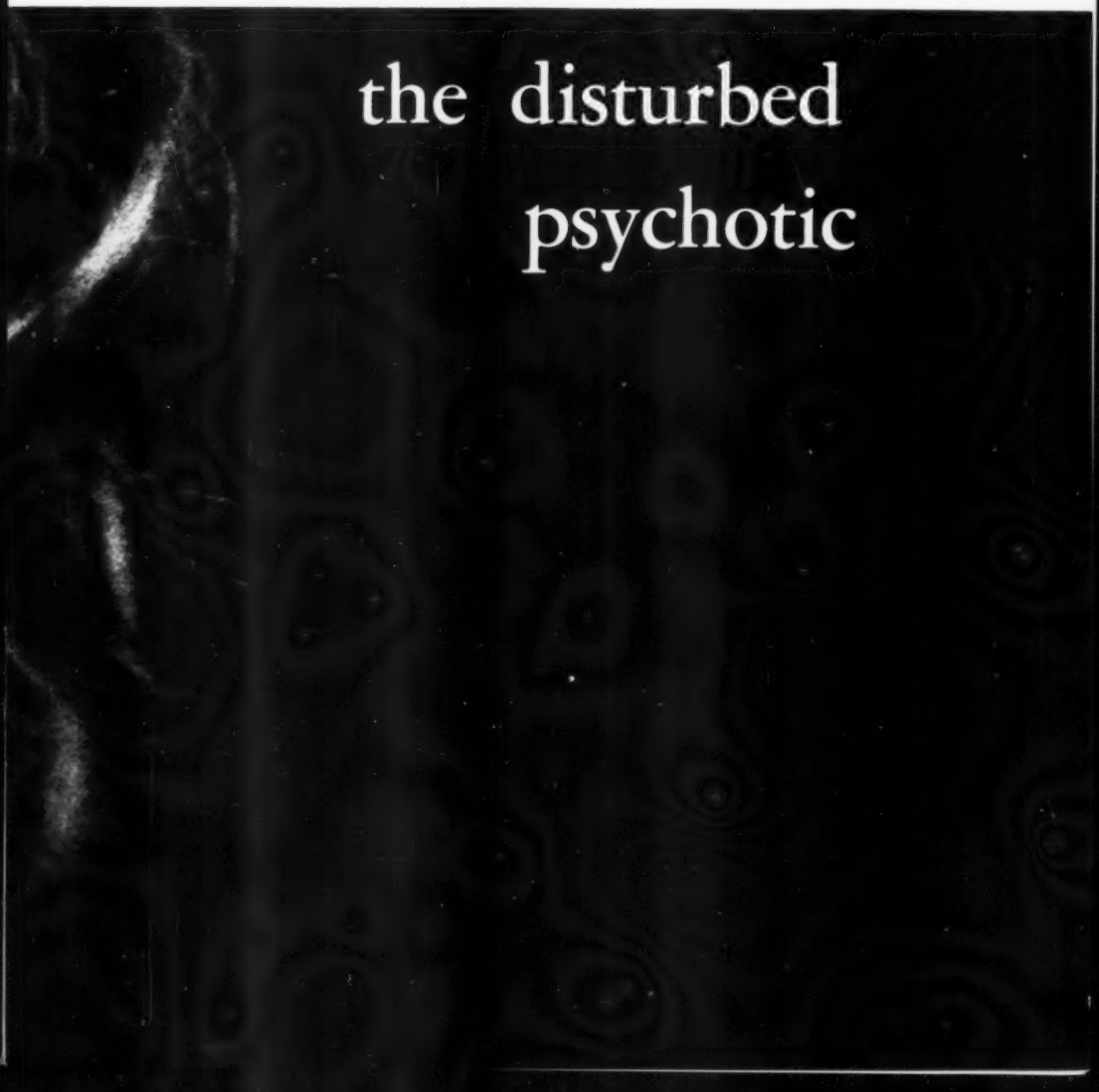

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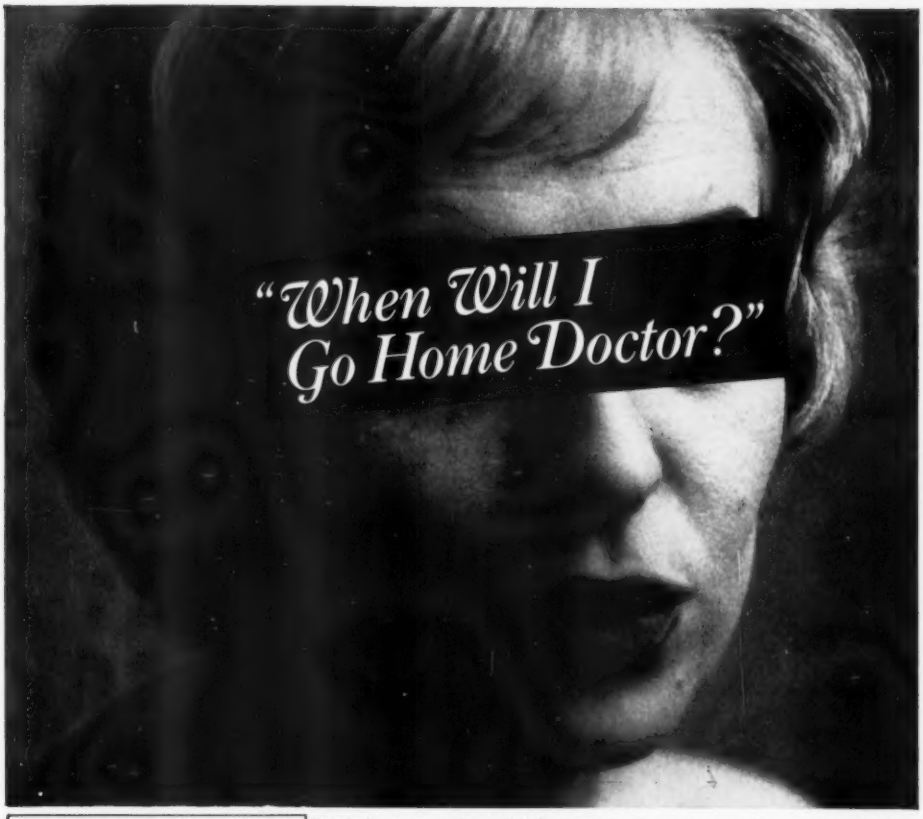

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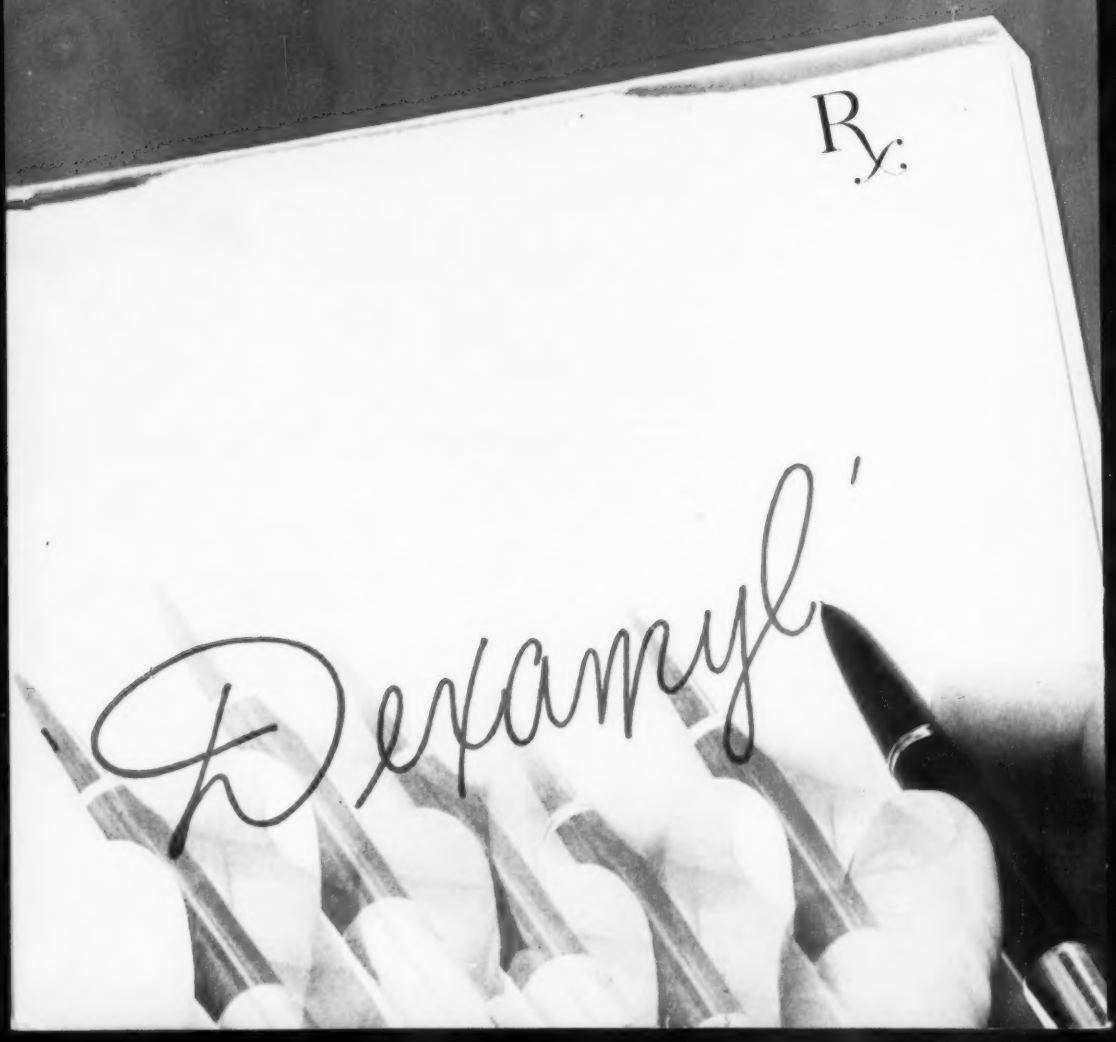
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